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Gender differences in patients with acute chest discomfort: a cross-sectional study

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3 **Gender differences in patients with acute chest discomfort: a cross-sectional study**
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13 **Competing interest statement**

14 All authors have completed the [Unified Competing Interest form](#) and declare no support from any
15 organization for the submitted work; no financial relationships with any organizations that might have
16 an interest in the submitted work in the previous three years, no other relationships or activities that
17 could appear to have influenced the submitted work.
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23 **Transparency declaration**

24 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and
25 transparent account of the study being reported; that no important aspects of the study have been
26 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been
27 explained.
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Abstract

Objectives To assess differences in symptoms predictive of acute coronary syndrome (ACS) between women and men presenting with chest discomfort in out-of-hours primary care (OHS-PC).

Design Cross-sectional study.

Setting Nine OHS-PC in the Netherlands.

Participants 993 women and 802 men who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2017.

Primary outcome measure Diagnosis of acute coronary syndrome (ACS). We compared patient and call characteristics of triage call recordings between women with and without ACS, and men with and without ACS. Diagnoses were retrieved from the patient's medical record in general practice, including hospital specialists' discharge letters.

Results Among 1,795 patients (mean age 58.8 (SD 19.5) years, 55.3% women), 15.0% of men and 8.6% of women had an ACS. In both sexes, retrosternal chest pain was discriminative for ACS (women with ACS vs. without 62.3% vs. 40.3%, $p=0.002$, men with ACS vs. without 52.5% vs. 39.7%, $p=0.032$), as was pressing/tightening pain (women 78.6% vs. 61.5%, $p=0.011$, men 82.1% vs. 57.4%, $p<0.001$) and radiation to arm (women 75.6% vs. 45.9%, $p<0.001$, men 56.0% vs. 34.8%, $p<0.001$). In women, severe pain (65.4% vs. 38.1%, $p=0.006$), a pale face (50.0% vs. 22.9%, $p=0.007$) and radiation to jaw (50.0% vs. 29.8%, $p=0.017$) were also discriminative for ACS, while in men this was sweating (52.4% vs. 38.1%, $p=0.015$), and against ACS stabbing pain (8.4% vs. 26.5%, $p<0.001$).

Ambulances were dispatched equally in women (72.9%) and men with ACS (70.0%).

Conclusion Symptoms predictive of ACS were rather similar for women and men with chest discomfort, with some important exceptions, such as severity, type, and radiation of pain, and some autonomous nervous system related symptoms.

Trial number: NTR7331

Keywords (5): acute coronary syndrome, gender, primary care, telephone triage, chest discomfort

Strengths and limitations of this study

- We could analyse the very initial conversation with symptom presentation of a large sample of patients calling for acute chest discomfort.
- We analysed the conversations without knowledge of the eventual diagnosis and therefore no hindsight bias of the researcher or recall bias of the patient could occur.
- Results are generalizable to comparable primary care settings in European countries, and our results may even be generalizable to emergency medical service (EMS, '112' or '911') settings.
- We had missing values on some clinical variables, a phenomenon common in routine care data.

Introduction

Adequate triage and early diagnosis is key in patients with acute chest discomfort because they might have an acute coronary syndrome (ACS) for which lifesaving early interventions are available. ACS is an umbrella term including ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).¹ Increased preventive measures and development of (timely) effective therapeutic interventions ('time is muscle') have resulted in improved outcomes and prognosis in ACS.² Telephone triage of patients with chest discomfort, as done in out-of-hours service primary care (OHS-PC) and emergency medical services (EMS or ambulance dispatch centres) is, however, challenging because it is difficult to differentiate ACS from other causes of chest discomfort based on symptoms only.^{3,4} Importantly, the majority of patients with chest discomfort (80%) in the Netherlands first approach the general practitioner (GP) or OHS-PC, and 20% directly calls the ambulance (112) or are self-referrals to the emergency department (ED).⁵

Previous hospital-based studies reported a delayed recognition of ACS in women compared to men.^{6,7} It was suggested that this delayed recognition was related to a less specific presentation in women.^{8,9} This caused an ongoing debate on whether women with ACS compared to men present with less specific symptoms, and how this affects diagnosis, but also treatment, and prognosis.^{10,11} A recent meta-analysis of 27 studies showed that women with ACS compared to men with ACS had higher odds of presenting with pain between the shoulder blades (OR 2.15, 95% CI 1.95-2.37), nausea or vomiting (OR 1.64, 95% CI 1.48-1.82) and shortness of breath (OR 1.34 (95% CI 1.21-1.48)).¹² Women with ACS had lower odds of sweating (OR 0.84, 95% CI 0.76-0.94) and presenting with chest pain (OR 0.70, 95% CI 0.63-0.78), but in both sexes chest pain remained the most common symptom (pooled prevalence men 79% and women 74%).¹² Importantly, researchers suggested standardization in methods of symptoms assessment is needed, because of the difficulties to formulate any definitive statements about symptom presentation, as studies assessed symptoms in different ways (questionnaires or abstracting from medical records).^{9,13-15} Abstracting symptom presentation from medical records may dilute symptom presentation, as they are translated by the clinician in medical terminology.¹⁶ Moreover, many studies suffer from recall or hindsight bias of both patient and researcher as they know the outcome (ACS).

For the clinician or telephone triage nurse it is crucial to differentiate ACS from other causes of chest discomfort. For that, studies are needed that include female and male patients presenting with chest discomfort, in which women and men who turn out to have ACS are compared to those who do not

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3 have ACS. Such studies are scarce. In a study performed among patients with chest discomfort seen at
4 the ED in the USA (77 women and 244 men with ACS, and 195 women and 240 men without ACS were
5 compared. Women with ACS more often reported arm pain than women without ACS (47% vs. 32%,
6 $p=0.021$), while men with ACS reported pressing feeling (63% vs. 54%, $p=0.035$) and chest pain (72% vs
7 60%, $p=0.005$) more often than men without ACS.¹³ In a recent Dutch OHS-PC study among 23 women
8 and 34 men with ACS, and 253 women and 208 men without ACS, differences in symptom presentation
9 between women and men were small.¹⁷ In men, radiation of pain (89.3% vs. 64.9%, $p\text{-value}=0.011$) was
10 discriminative for ACS, while stabbing chest pain (3.7% vs. 24.0%, $p\text{-value}=0.014$) was discriminative for
11 the absence of ACS. Both these symptoms were not discriminative in women (90.0% vs 78.6%, $p=0.227$,
12 and 15.8% vs. 18.8%, $p=0.743$), respectively.¹⁷

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21 We aimed to assess symptoms predictive of ACS in women and men separately, among patients
22 presenting with acute chest discomfort to OHS-PC based on analyses of recorded telephone triage
23 conversations.
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26 27 28 **Methods**

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30 We performed a cross-sectional study with a random sample of 1,795 OHS-PC calls for chest discomfort
31 (chest pain, pressure, tightness, or discomfort) between 2014 and 2016.¹⁸ We first selected calls on the
32 basis of International Code for Primary Care (ICPC; a WHO world-wide code system for primary care)
33 codes (K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98) and keywords (thoracic pain,
34 chest pain, myocardial infarction, heart attack and their common abbreviations).^{19,20} On purpose, we
35 sampled a broad variety of symptoms to capture the entire domain of patients that could be suspected
36 of ACS. We drew a random sample of all available calls of these patients with the Random Number
37 Generator (RAND) function in Microsoft Excel. Calls were excluded before re-listening when the
38 patients' age was below 18 years or when the patient did not live in the surrounding area of the OHS-
39 PCs (because then we could not retrieve a diagnosis from the general practitioner of these patients).
40 Calls were excluded during re-listening when it not concerned a triage call (e.g. inter-collegial
41 consultation) or when the recording was of poor quality.
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52 We re-listened the telephone triage recordings and collected information about patient and
53 conversation characteristics, on symptom presentation, medical history, urgency allocation, and
54 involvement of a supervising general practitioner (GP) in the triage. Nine OHS-PC in the Netherlands
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3 participated, serving a total population of 1.5 million people. The final diagnoses were provided by the
4 patients' GP, and this was based on the electronic medical file including ED and cardiologist discharge
5 letters, and also notes from the OHS-PC. An ACS was based on the cardiologist's diagnosis, including
6 information on levels of (high-sensitivity) troponin and electrocardiography results.
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10 11 Context

12 In the Netherlands, OHS-PC covers primary care during 73% of the week hours, and the initial contact is
13 by telephone. In most OHS-PC and EMS, the 'Netherlands Triage Standard' (NTS) is used as a decision
14 support to classify the urgency of the patients' conditions.²¹ Based on the patient's symptom
15 presentation, the triage nurse needs to choose the most appropriate complaint out of 56 'main
16 complaints'. Each NTS 'main complaint' incorporates a decision tree with hierarchically ordered
17 questions, which are similar for men and women. Triage nurses fill out the caller's responses in the
18 semi-automatic NTS system, which then generates urgency allocations (U0 (reanimation) to U5 (self-
19 care advice, see also appendix-table1). The triage nurse can overrule this recommendation and up- or
20 downscale the urgency allocation, often after consulting the supervising GP.²² Since its introduction in
21 2011, the NTS system has, however, never been formally validated by correlating the generated
22 urgencies to clinical endpoints.²¹
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33 Data analyses

34 We compared patient and call characteristics between women with and without ACS, and men with and
35 without ACS. We analysed the association between urgency allocation and the final diagnosis ACS (with
36 or without other life threatening events (LTEs)). We considered pulmonary embolism, thoracic aortic
37 dissection and acute abdominal aneurysm as LTEs; patients with LTEs as well as those with ACS should
38 receive an U1-level urgency (full list in table 2).
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45 For comparison of dichotomous variables we used the Chi² test or Fisher exact test and for continuous
46 variables the independent sample t-test or Mann-Whitney U test. Data analysis was performed using
47 SPSS, IBM version 25.
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51 Patient and public involvement

52 No patients were involved in setting the research question or the outcome measures, or in developing
53 plans for design, however, they were involved in the implementation of the study. In addition, they
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3 were asked to advise on interpretation and writing up of results. Results will be shared and discussed
4 with the national patient community of cardiovascular diseases ('Hartraad').
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8 Ethics

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10 The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics
11 Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the
12 Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to
13 subjects and could otherwise not be carried out logistically. Personal and research data were handled
14 and stored according to the European General Data Protection Regulation.
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19 **Results**

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21 Among the 1,795 callers with chest discomfort (mean age 58.8 (SD 19.5) years, 55.3% women), 8.6% of
22 women and 15.0% of men had an ACS. In women with an ACS, 18.8% had a STEMI, 48.2% a NSTEMI,
23 20.0% an UAP, and 13.0% non-classified ACS. In men with ACS, 32.5% had a STEMI, 36.7% a NSTEMI,
24 27.5% an UAP, and 3.3% non-classified ACS.
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28 A total of 22 (2.2%) women and 23 men (2.9%) had another LTE than ACS (e.g. pulmonary embolism,
29 thoracic aortic dissection, acute abdominal aneurysm, acute heart failure).
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33 *Patient and call characteristics*

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35 In table 1, patient and call characteristics are presented for women and men with and without ACS.
36 Men and women with ACS were older than those without ACS (mean age of women 73.6 vs. 57.8 years,
37 $p < 0.001$, men 67.2 vs. 56.9 years, $p < 0.001$), and the mean duration of the telephone calls shorter
38 (women 6:47 vs. 7:47 minutes, $p = 0.021$, men 6:31 vs. 7:33 minutes, $p = 0.004$).
39
40 The GP was consulted by the triage nurse in the majority of cases (52.2% in women and 55.5% in men,
41 $p = 0.161$). However, in women with ACS, the GP was less often consulted than in women without ACS
42 (41.2% vs. 53.2%, $p = 0.034$). In men such a difference was not observed (53.3% vs. 55.9%, $p = 0.607$).
43
44 In around half of the calls, someone else called on behalf of the patient; somewhat less often in women
45 than in men (49.5% vs. 54.7%, $p = 0.029$). In cases with ACS, for both sexes more often someone else
46 called than in those without ACS (in women 69.4% vs. 47.7%, $p < 0.001$, in men 65.8% vs. 52.8%,
47 $p = 0.008$). In men with ACS, most often their female partner (53.3%) called, while in women with ACS, it
48 was either their male partner (17.6%), their daughter (20.0%) or a nurse (17.6%). See appendix-table 2.
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3 Callers expressed concerns in nearly all calls, also in those without an ACS; women with ACS vs. women
4 without ACS 97.3% vs. 88.9% ($p=0.109$), and men with ACS vs. men without ACS 96.3% vs. 86.5%
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6 ($p=0.041$).

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8 Both women and men with ACS more often had a history of cardiovascular disease or cardiovascular risk
9 factors (e.g. hypertension and diabetes) than those without (women 78.3% vs. 57.5%, $p=0.001$, and in
10 men these proportions were 72.1% vs. 61.9% ($p=0.046$), respectively.

14 15 *Symptom presentation*

16 Chest pain was the most common complaint, both in those with and without an ACS; in women with and
17 without ACS 98.8% and 93.1% ($p=0.055$), and in men 92.4% and 94.5%, respectively ($p=0.364$).

18
19 Retrosternal located chest pain was more common in women and men with ACS than in those without
20 ACS (women 62.3% vs. 40.3%, $p=0.002$, and men 52.5% vs. 39.7%, $p=0.032$). Also, radiation of pain to
21 the arms seemed indicative of ACS in both sexes (women with vs. without ACS 75.6% vs. 45.9%, $p<0.001$,
22 and men 56.0% vs. 34.8%, $p<0.001$), as was pressing/heavy/tightening chest pain (women with vs.
23 without ACS 78.6% vs. 61.5%, $p=0.011$ and men 82.1% vs. 57.4%, $p<0.001$). Only in women radiation to
24 the jaw (50.0% vs. 22.9%, $p=0.007$) and severe pain (8 or more on a Numeric Rating Scale 0-10) was
25 indicative for ACS (65.4% vs. 38.1, $p=0.006$). Only in men, stabbing pain was discriminative in that it was
26 very rare in those with ACS (8.4% vs. 26.5%, $p<0.001$).

27
28 Of the autonomous nervous system (ANS)-related symptoms, nausea/vomiting and dizziness/near
29 fainting were not indicative for ACS in either sex, with the exception of a pale face that was
30 discriminative in women (50.0% vs. 29.8%, $p=0.017$), and sweating in men (52.4% vs. 38.1%, $p=0.015$).
31
32 Recognition of symptoms being similar to a previous cardiac event was discriminative for ACS in men
33 (52.9% vs. 32.1%, $p=0.004$), but not clearly for ACS in women (32.5% vs. 21.4%, $p=0.108$).

34 35 36 37 38 39 40 41 42 43 *Diagnoses*

44 The most common non-ACS diagnoses in both sexes were (i) non-urgent cardiovascular diseases such as
45 stable angina pectoris, stable heart failure and arrhythmias (19.5% of all female callers with chest
46 discomfort vs. 21.2% of male callers, $p=0.384$) and (ii) non-cardiac unspecified chest pain (women 16.4%
47 vs. 19.8% men, $p=0.061$). Women more often than men were diagnosed with musculoskeletal problems
48 (women 20.8% vs. men 14.1%, $p=0.001$) and psychogenic conditions (women 14.0% vs. men 8.4%,
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60 $p<0.001$).

Urgencies

Women and men were equally sent an ambulance; overall (43.6% vs. 46.6%, $p=0.200$). These proportions were in women compared to men with ACS or other LTEs 66.4% vs. 67.1%, $p=0.897$).

Women and men in whom ACS was diagnosed had more often ambulances dispatched than in those showed not to have an ACS (women 72.9% vs. 40.9%, $p<0.001$, and men 70.0% vs. 42.5%, $p<0.001$). See table 3.

Discussion

For both sexes, retrosternal pain, pain described as pressing, heavy or tightening, and radiation to the arm were indicative of ACS in patients presenting with chest discomfort to out-of-hours primary care (OHS-PC). Radiation of pain to the jaw, severe pain, and a pale face was indicative for ACS in women. Sweating was positive related to ACS and stabbing pain negatively in men with chest discomfort. Women and men were equally often sent an ambulance.

Our finding that radiation of pain to the arm and chest pressure were discriminative for ACS in both sexes was not reported in the two previous studies that assessed ACS symptoms using the same methodology. The US study in ED-setting found that radiation to the arm was indicative for ACS in women but not for men, and chest pressure was distinctive for men but not for women.¹³ The OHS-PC study reported opposite that radiation to the arm was indicative for ACS in men, but not in women, and reported similar to our study that stabbing pain is very uncommon in men with ACS.¹⁷

Regarding dispatching the ambulance, the aforementioned OHS-PC study and two EMS studies showed, similar to our findings, that there was no difference in dispatch priorities between men and women with ACS.^{4, 17, 23} This is in contrast with studies that show delay in hospital presentation of women with ACS.^{9, 24}

We need to realize that focusing on differences may blur the large overlap in symptoms. Moreover, comparing *selectively* women with ACS to men with ACS as many previous studies did, is clinically irrelevant.^{9, 14, 25} Clinicians, including GPs, and triage nurses need to know whether and how women with ACS differ from women without ACS, with the same question for men. Nevertheless, even guidelines stick to comparing those with established disease, and express the view that women with ACS more likely present with less specific symptoms than men with ACS.^{1, 26} Unfortunately, public awareness campaigns follow this reasoning, and over-emphasize sex differences in women awareness campaigns

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3 ('Go Red for Women' in the United States and 'Invisible me' in Australia).^{7, 25, 27} Unbalanced attention to
4 differences, neglecting the much larger overlap may even introduce new blind spots in recognizing ACS
5 in women.²⁸
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10 A likely reason behind the predominant message that women present with other ACS symptoms than
11 men is the difference in pathophysiology of coronary artery disease. Women compared to men more
12 often have elongated plaques, located on bifurcations in epicardial coronaries, coronary spasm,
13 microvascular dysfunction, and spontaneous coronary dissection.^{27, 29} These pathophysiological
14 differences have an effect on interventional treatment and prognosis.^{2, 29} However, these differences
15 do not necessarily imply an effect on symptom presentation because the pain pathway is equal in
16 women and men: i.e. triggered by myocardial ischemia.^{30, 31} A supply and demand mismatch of the
17 myocardial oxygen consumption triggers sensory nerve endings in the myocardium and cause ischemia
18 symptoms, and this is irrespective of the fact whether the ischemia is caused by a plaque rupture in an
19 epicardial artery or spasm, or any other cause.³¹ The sex differences in pathophysiology of ACS do
20 therefore not support the belief in differences in ACS symptoms between women and men.
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30 Another reason behind the belief of 'vague' symptom presentation in women with ACS might be that
31 they seem to present a larger number of symptoms than men with ACS, and this may be interpreted as
32 'vague' by physicians.^{15, 32} The presentation of multiple symptoms may influence the prompt
33 recognition of heart disease and initial actions on the part of providers.^{32, 33} In a study from 2018, 2009
34 women and 976 men hospitalized for myocardial infarction, healthcare providers initially thought
35 symptoms of women (53.4%) were less often heart-related than in men (36.7%).³² Women and men
36 had the same chest pain symptoms, but women reported more additional symptoms.³²
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40 In our study, the call duration and the number of GP consultations by the triage nurse were similar
41 among women and men, suggesting that triage nurses seem not to experience more difficulties in
42 interpreting symptoms in women than men. This is in line with a prospective study with 2,795 patients
43 with chest discomfort in ED-setting that showed the physicians' diagnostic uncertainty for the presence
44 of ACS in women was not more common as compared to men.³⁴
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50 Interestingly, in the majority of calls in our study someone else than the patient called the OHS-PC
51 (women with ACS 69.4%, without ACS 47.7%, and men with ACS 65.8%, and without ACS 52.8%). This
52 was also highlighted in an Australian study among 1,681 patients with an acute myocardial infarction; in
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3 90.5% of the women with AMI someone else called on behalf of the patient and in 87.8% of the men
4 with AMI. ³⁵
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8 9 *Strengths and limitations*

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11 We could analyse the very initial conversation with symptom presentation of a large sample of patients
12 calling the OHS-PC because of chest discomfort. We analysed the conversation without knowledge of
13 the eventual diagnosis (no hindsight bias of the researcher or recall bias of the patient). Another
14 strength is that our results are generalizable to comparable primary care settings, e.g. UK and
15 Scandinavian countries, and some other European countries. Our results may even be generalizable to
16 EMS settings, since the prior probability of having an ACS is comparable in EMS setting as in OHS-PC
17 settings. ⁴
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20 We had missing values on some clinical variables, a phenomenon common in routine care data.
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24 25 **Conclusions**

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28 Symptoms predictive of ACS were rather similar for women and men with chest discomfort, with some
29 important exceptions, such as severity, type, and radiation of pain, and some autonomous nervous
30 system related symptoms.
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Data sharing statement

The data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution

FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DC conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript. DC, EdG, AH and RD contributed with and approved the final version of the manuscript.

References

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S and Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016;37:267-315.
2. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA and Eagle KA. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20-6.
3. Burman RA, Zakariassen E and Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice*. 2014;15:51.
4. Rawshani A, Larsson A, Gelang C, Lindqvist J, Gellerstedt M, Bang A and Herlitz J. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology*. 2014;176:859-65.
5. Mol KA, Smoczynska A, Rahel BM, Meeder JG, Janssen L, Doevendans PA and Cramer MJ. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart*. 2018;5:e000859.
6. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, Sullivan MD, DeLong ER, Bradley EH, Krumholz HM and Peterson ED. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. *Archives of internal medicine*. 2010;170:1834-41.
7. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J and Zaman S. Sex Differences Persist in Time to Presentation, Revascularization, and Mortality in Myocardial Infarction Treated With Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2019;8:e012161.
8. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G and Zheng ZJ. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama*. 2012;307:813-22.
9. Chen W, Woods SL and Puntillo KA. Gender differences in symptoms associated with acute myocardial infarction: a review of the research. *Heart Lung*. 2005;34:240-7.
10. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ and Long T. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Archives of internal medicine*. 2007;167:2405-13.
11. Sorensen NA, Neumann JT, Ojeda F, Schafer S, Magnussen C, Keller T, Lackner KJ, Zeller T, Karakas M, Munzel T, Blankenberg S, Westermann D and Schnabel RB. Relations of Sex to Diagnosis and Outcomes in Acute Coronary Syndrome. *J Am Heart Assoc*. 2018;7.
12. van Oosterhout REM, de Boer AR, Maas A, Rutten FH, Bots ML and Peters SAE. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc*. 2020;9:e014733.
13. Devon HA, Rosenfeld A, Steffen AD and Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *J Am Heart Assoc*. 2014;3:e000586.
14. Araujo C, Laszczynska O, Viana M, Melao F, Henriques A, Borges A, Severo M, Maciel MJ, Moreira I and Azevedo A. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. *BMJ open*. 2018;8:e018798.
15. Canto JG, Canto EA and Goldberg RJ. Time to standardize and broaden the criteria of acute coronary syndrome symptom presentations in women. *Can J Cardiol*. 2014;30:721-8.

16. Ferry AV, Anand A, Strachan FE, Mooney L, Stewart SD, Marshall L, Chapman AR, Lee KK, Jones S, Orme K, Shah ASV and Mills NL. Presenting Symptoms in Men and Women Diagnosed With Myocardial Infarction Using Sex-Specific Criteria. *J Am Heart Assoc.* 2019;8:e012307.
17. van der Meer MG, Appelman Y, Rutten KHG, van der Graaf Y, Nathoe HM, Doevendans PA, Smit M, Verheij E, Botermans A and Rutten FH. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open.* 2019;9:e031613.
18. Erkelens DC, Wouters LT, Zwart DL, Damoiseaux RA, De Groot E, Hoes AW and Rutten FH. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open.* 2019;9:e027477.
19. Soler JK, Okkes I, Wood M and Lamberts H. The coming of age of ICPC: celebrating the 21st birthday of the International Classification of Primary Care. *Family practice.* 2008;25:312-7.
20. Olagundoye OA, Malan Z, Mash B, van Boven K, Gusso G and Ogunnaike A. Reliability measurement and ICD-10 validation of ICPC-2 for coding/classification of diagnoses/health problems in an African primary care setting. *Family practice.* 2018;35:406-411.
21. van Ierland Y, van Veen M, Huibers L, Giesen P and Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Family practice.* 2011;28:334-41.
22. Keizer E, Maassen I, Smits M, Wensing M and Giesen P. Reducing the use of out-of-hours primary care services: A survey among Dutch general practitioners. *The European journal of general practice.* 2016;22:189-95.
23. Herlitz J, Starke M, Hansson E, Ringvall E, Karlson BW and Waagstein L. Characteristics and outcome among women and men transported by ambulance due to symptoms arousing suspicion of acute coronary syndrome. *Med Sci Monit.* 2002;8:CR251-6.
24. Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, Zdravkovic M, Milicic D, Dilic M, Manfrini O, Koller A and Badimon L. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc.* 2017;6.
25. Diercks DB, Owen KP, Kontos MC, Blomkalns A, Chen AY, Miller C, Wiviott S and Peterson ED. Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (NCDR ACTION Registry-GWTG). *American heart journal.* 2010;160:80-87 e3.
26. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on Quality of C and Outcomes R. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. *Circulation.* 2016;133:916-47.
27. Khamis RY, Ammari T and Mikhail GW. Gender differences in coronary heart disease. *Heart.* 2016;102:1142-9.
28. Amalberti R. *Navigating safety: necessary compromises and trade-offs – theory and practice.* Heidelberg: Springer; 2013.
29. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas AHEM, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V, EUGenMed and Grp CCS. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *European heart journal.* 2016;37:24-+.
30. Leach A and Fisher M. Myocardial ischaemia and cardiac pain - a mysterious relationship. *Br J Pain.* 2013;7:23-30.

- 1
2
3 31. Rosen SD. From heart to brain: the genesis and processing of cardiac pain. *Can J Cardiol.* 2012;28:S7-19.
4
5 32. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA
6 and D'Onofrio G. Sex Differences in the Presentation and Perception of Symptoms Among Young
7 Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of
8 Gender on Outcomes of Young AMI Patients). *Circulation.* 2018;137:781-790.
9
10 33. Goldberg R, Goff D, Cooper L, Luepker R, Zapka J, Bittner V, Osganian S, Lessard D, Cornell C,
11 Meshack A, Mann C, Gilliland J and Feldman H. Age and sex differences in presentation of symptoms
12 among patients with acute coronary disease: the REACT Trial. Rapid Early Action for Coronary
13 Treatment. *Coron Artery Dis.* 2000;11:399-407.
14
15 34. Hillinger P, Twerenbold R, Wildi K, Rubini Gimenez M, Jaeger C, Boeddinghaus J, Nestelberger T,
16 Grimm K, Reichlin T, Stallone F, Puelacher C, Sabti Z, Kozhuharov N, Honegger U, Ballarino P, Miro O,
17 Denhaerynck K, Ekrem T, Kohler C, Bingisser R, Osswald S and Mueller C. Gender-specific uncertainties in
18 the diagnosis of acute coronary syndrome. *Clin Res Cardiol.* 2017;106:28-37.
19
20 35. Coventry LL, Bremner AP, Jacobs IG and Finn J. Myocardial infarction: sex differences in
21 symptoms reported to emergency dispatch. *Prehosp Emerg Care.* 2013;17:193-202.
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Table 1. Baseline characteristics of 993 (55.3%) women and 802 (44.7%) men patients contacting the OHS-PC with chest discomfort (pain, pressure, tightness, or discomfort)

Characteristics	993 women			802 men		
	ACS N = 85 (8.6%)	No ACS N = 908 (91.4%)	p-value	ACS N = 120 (15.0%)	No ACS N = 682 (85.0%)	p-value
Mean age in years (SD)	73.6 (±14.1)	57.8 (±20.1)	<0.001	67.2 (±13.0)	56.9 (±19.2)	<0.001
Call characteristics						
Mean call duration in min (SD)	6:47 (±5:16)	7:47 (±3:48)	0.021	6:31 (±3:13)	7:33 (±3:42)	0.004
Mean patient's introduction duration in min (SD)	0:14 (±0:08)	0:19 (±0:13)	<0.001	0:16 (±0:11)	0:19 (±0:14)	0.060
Triage nurse consulted the GP	35 (41.2)	483 (53.2)	0.034	64 (53.3)	381 (55.9)	0.607
Someone else called on behalf of patient	59 (69.4)	433 (47.7)	<0.001	79 (65.8)	360 (52.8)	0.008
The patient or person who called expressed concerned (n=497;425)	36 (97.3)	409 (88.9)	0.109	52 (96.3)	321 (86.5)	0.041
Chest pain (n=960;779)	81 (98.8)	817 (93.1)	0.055	110 (92.4)	624 (94.5)	0.364
Severe Pain (>7 on a scale 0-10) (412;341)	17 (65.4)	147 (38.1)	0.006	13 (23.6)	87 (30.4)	0.312
Duration						
> 15 min (n=827;674)	66 (100)	729 (95.8)	0.102	99 (97.1)	541 (94.6)	0.292
< 12 hrs (n=861;702)	60 (85.7)	575 (72.7)	0.018	88 (81.5)	431 (72.6)	0.052
Location (n=706;561)*						
Retrosternal	33 (62.3)	263 (40.3)	0.002	42 (52.5)	191 (39.7)	0.032
Right or left side thorax	14 (26.4)	260 (39.8)	0.054	26 (32.5)	211 (43.9)	0.057
Type of pain (n=744;590)**						
Pressing/heavy/tightening	44 (78.6)	423 (61.5)	0.011	78 (82.1)	284 (57.4)	<0.001
Stabbing	8 (14.3)	155 (22.5)	0.152	8 (8.4)	131 (26.5)	<0.001
Radiation of chest pain (n=778;613) ***						

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3 Any location	61 (85.9)	485 (68.6)	0.002	65 (63.7)	292 (57.1)	0.218
4						
5 Arm	31 (75.6)	188 (45.9)	<0.001	47 (56.0)	117 (34.8)	<0.001
6						
7 Between the shoulder blades	11 (52.4)	159 (41.7)	0.336	14 (27.5)	91 (29.4)	0.781
8						
9 Jaws	10 (50.0)	66 (22.9)	0.007	1 (2.6)	28 (11.6)	0.146
10						
11 Shortness of breath (n=751;614)	47 (72.3)	455 (66.3)	0.328	53 (60.9)	329 (62.4)	0.788
12						
13 Symptoms similar to previous cardiac	13 (32.5)	79 (21.4)	0.108	27 (52.9)	92 (32.1)	0.004
14 events (n=410;338)						
15						
16						
17 ANS-related symptoms						
18						
19 Sweating (n=607;523)	28 (49.1)	234 (42.5)	0.340	43 (52.4)	168 (38.1)	0.015
20						
21 Nausea or vomiting (n=463;345)	16 (44.4)	240 (56.2)	0.173	27 (45.8)	122 (42.7)	0.661
22						
23 Pallor (n=339;295)	17 (50.0)	91 (29.8)	0.017	20 (40.8)	82 (33.)	0.315
24						
25 Dizziness or near fainting (879;720)	13 (18.6)	197 (24.4)	0.277	17 (15.9)	127 (20.2)	0.249
26						
27 Medical history						
28						
29 CV disease or risk factors (n=777;684)	54 (78.3)	407 (57.5)	0.001	75 (72.1)	359 (61.9)	0.046
30						
31 Coronary artery disease (n=494;472)	17 (42.5)	114 (25.1)	0.017	45 (57.0)	151 (38.4)	0.002
32						
33 Hypertension (n=435;321)	22 (71.0)	142 (35.1)	<0.001	17 (47.2)	94 (33.0)	0.091
34						
35 Diabetes mellitus (n=412;333)	12 (41.4)	56 (14.6)	<0.001	12 (28.6)	59 (20.3)	0.220
36						
37 Hypercholesterolemia or use of statins	8 (36.4)	81 (23.2)	0.161	19 (45.2)	62 (23.3)	0.003
38						
39 (n=371;308)						
40						

41 *P-value comparing retrosternal or left/right side thorax vs. others locations of pain together (retrorsternal, left/right side thorax,
42 back/shoulder, epigastric region)

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45 * Pressing/ heavy/tightening pain vs. other types of pain (stabbing, burning, cramping, tearing). Stabbing pain: stabbing vs. other types of
46 pain (pressing/heavy/tightening, burning, cramping, tearing)

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48 *** P-value comparing radiation arm or back/shoulder or jaws vs. no radiation

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50 NRS: Numeric Rating Scale

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52 ANS-related symptoms: Autonomous nervous system related symptoms

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54 CV disease or risk factors; a history of previous coronary artery disease, heart failure, stroke, cardiac arrhythmia, hypertension, and/or
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3 diabetes (patient reported)
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5 Coronary artery disease: History of prior MI, PCI, CABG, stable or unstable angina pectoris (patient reported)
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Table 2. Diagnosis of 1,795 patients who contacted the OHS-PC for chest discomfort (pain, pressure, tightness, or discomfort), divided in women and men

	Women n= 993 (55.3%)	Men n=802 (44.7%)	p-value
Acute coronary syndrome	85 (8.6)	120 (15.0)	<0.001
STEMI	16 (18.8)	39 (32.5)	0.037
NSTEMI	41 (48.2)	44 (36.7)	0.114
UAP	17 (20.0)	33 (27.5)	0.250
Non-classified ACS	11 (13.0)	4 (3.3)	0.013
Life threatening events (LTE's)	22 (2.2)	23 (2.9)	0.448
Pulmonary embolism	6 (27.3)	7 (30.4)	0.815
Thoracic aortic dissection	4 (18.2)	2 (8.7)	0.349
Acute abdominal aneurysm	3 (13.6)	2 (8.7)	0.598
Other*	9 (40.9)	12 (52.2)	0.449
Non-urgent cardiovascular diseases**	194 (19.5)	170 (21.2)	0.384
Non-cardiac chest pain, not further specified ***	163 (16.4)	159 (19.8)	0.061
Musculoskeletal pain	199 (20.0)	113 (14.1)	0.001
Psychogenic disorders	139 (14.0)	67 (8.4)	<0.001
Gastrointestinal tract disorders	76 (7.7)	62 (7.7)	0.951
Respiratory tract disorders	52 (5.2)	45 (5.6)	0.727
Other non-urgent diagnoses***	63 (6.3)	43 (5.4)	0.380
<p>*Acute heart failure, stroke, severe COPD exacerbation, sepsis, coronary spasm probably caused by hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.</p> <p>** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension</p>			

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3 *** Cardiac pathology unlikely after cardiologist's diagnostic work-up, but without differential diagnosis
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5 **** Amongst others: anemia, malignancy, vasovagal collapse, side effects medication, dermatologic diseases
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Table 3. Association between urgency allocation, diagnose ACS and other life threatening events (LTE)

Women	ACS n=85 (8.6%)	No ACS n=908 (91.4%)	p-value 1*	p-value 2**
U1	62 (72.9)	371 (40.9)	<0.001	<0.001
U2	12 (14.1)	231 (25.4)		
U3-U5	11 (13.0)	306 (33.6)		
Men	ACS n=120 (15.0%)	No ACS n=682 (85.0%)		
U1	84 (70.0)	290 (42.5)	<0.001	<0.001
U2	19 (15.8)	142 (20.8)		
U3-U5	17 (14.2)	250 (36.7)		
Women	ACS or LTE n=107 (10.8%)	No ACS or LTE n=886 (89.2%)		
U1	71 (66.4)	362 (40.9)	<0.001	<0.001
U2	21 (19.6)	222 (25.1)		
U3-U5	15 (14.0)	302 (34.0)		
Men	ACS or LTE n=143 (17.8%)	No ACS or LTE n=659 (82.2%)		
U1	96 (67.1)	278 (42.2)	<0.001	<0.001
U2	24 (16.8)	137 (20.8)		
U3-U5	23 (16.1)	244 (37.0)		
<p>* P-value 1: U1 vs. U2, U3, U4 and U5</p> <p>** P-value 2: U1,U2 vs. U3,U4,U5</p> <p>***LTE = life threatening event. Life threatening events consist of: ACS; pulmonary embolism; thoracic aortic dissection; acute heart failure; stroke; abdominal aortic aneurysm; severe COPD exacerbation; diabetic ketoacidosis; coronary spasm probably caused by hypokalaemia; epileptic insult; bleeding from oesophageal varices; ovarian torsion; ventricular fibrillation.</p>				

APPENDIX**Appendix-Table 1: Urgency levels**

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advice given by triage nurse

Appendix-Table 2: Relation of caller to patient in women and men with ACS

	Women n= 85 (8.6%)	Men n = 120 (15.0%)	P-value
Someone else calls on behalf of patient	59 (69.4)	79 (65.8)	0.590
Partner	16 (18.8)	64 (53.3)	<0.001
Son, daughter or other family member	20 (23.5)	8 (6.7)	0.001
Nurse	15 (17.6)	4 (3.3)	<0.001
Other (neighbor, friend, colleague)	8 (9.4)	3 (2.5)	0.030

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
/Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8

		(b) Report category boundaries when continuous variables were categorized	7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Gender differences in patients with acute chest discomfort: a cross-sectional study

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3 **Gender differences in patients with acute chest discomfort: a cross-sectional study**
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19 All authors take responsibility for all aspects of the reliability and freedom from bias of the data
20 presented and their discussed interpretation
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13 **Competing interest statement**

14 All authors have completed the Unified Competing Interest form and declare no support from any
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23 **Transparency declaration**

24 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and
25 transparent account of the study being reported; that no important aspects of the study have been
26 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been
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Abstract

Objectives To assess differences in symptom presentation of women with and without an acute coronary syndrome (ACS), and the same in men, in patients with chest discomfort who contact out-of-hours primary care (OHS-PC).

Design Cross-sectional study.

Setting Nine OHS-PC in the Netherlands.

Participants 993 women and 802 men who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2016.

Primary outcome measure Diagnosis of ACS. We compared patient and call characteristics of triage call recordings between women with and without ACS, and men with and without ACS. Diagnoses were retrieved from the patient's medical record in general practice, including hospital specialists' discharge letters.

Results Among 1,795 patients (mean age 58.8 (SD 19.5) years, 55.3% women), 15.0% of men and 8.6% of women had an ACS. In both sexes, retrosternal chest pain was associated with ACS (women with ACS vs. without 62.3% vs. 40.3%, $p=0.002$, men with ACS vs. without 52.5% vs. 39.7%, $p=0.032$), as was pressing/tightening pain (women 78.6% vs. 61.5%, $p=0.011$, men 82.1% vs. 57.4%, $p<0.001$) and radiation to arm (women 75.6% vs. 45.9%, $p<0.001$, men 56.0% vs. 34.8%, $p<0.001$). In women, severe pain (65.4% vs. 38.1%, $p=0.006$), a pale face (50.0% vs. 22.9%, $p=0.007$) and radiation to jaw (50.0% vs. 29.8%, $p=0.017$) were also associated with ACS, while in men this was sweating (52.4% vs. 38.1%, $p=0.015$), and against ACS stabbing pain (8.4% vs. 26.5%, $p<0.001$).

Ambulances were dispatched equally in women (72.9%) and men with ACS (70.0%).

Conclusion There were more similarities than differences in symptoms associated with the diagnosis ACS for women and men. Important exceptions were severity, type, and radiation of pain, and in women a pale face, and in men sweating.

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3 **Trial number:** NTR7331
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5 **Keywords (5):** acute coronary syndrome, gender, primary care, telephone triage, chest discomfort
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9 **Strengths and limitations of this study**
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- 11 • We could analyse the very initial conversation with symptom presentation of a large sample of
12 patients calling for acute chest discomfort.
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- 14 • We analysed the conversations without knowledge of the eventual diagnosis and therefore no
15 hindsight bias of the researcher or recall bias of the patient could occur.
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- 17 • Results are generalizable to comparable primary care settings in the United Kingdom and
18 Scandinavian Countries, and our results may even be generalizable to emergency medical
19 service (EMS, '112' or '911') settings.
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- 21 • We had missing values on some clinical variables, a phenomenon common in routine care data.
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Introduction

Adequate triage and early diagnosis is key in patients with acute chest discomfort because they might have an acute coronary syndrome (ACS) for which lifesaving early interventions are available. ACS is an umbrella term including ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).¹ Increased preventive measures and development of (timely) effective therapeutic interventions ('time is muscle') have resulted in improved outcomes and prognosis in ACS.² Telephone triage of patients with chest discomfort, as done in out-of-hours service primary care (OHS-PC) and emergency medical services (EMS or ambulance dispatch centres) is, however, challenging because it is difficult to differentiate ACS from other causes of chest discomfort based on symptoms only.^{3,4} Importantly, the majority of patients with chest discomfort (80%) in the Netherlands first approach the general practitioner (GP) or OHS-PC, and 20% directly calls the ambulance (112) or are self-referrals to the emergency department (ED).⁵

Previous hospital-based studies reported a delayed recognition of ACS in women compared to men.^{6,7} It was suggested that this delayed recognition was related to a less specific presentation in women.^{8,9} This caused an ongoing debate on whether women with ACS compared to men present with less specific symptoms, and how this affects diagnosis, but also treatment, and prognosis.^{10,11} A recent meta-analysis of 27 studies showed that women with ACS compared to men with ACS had higher odds of presenting with pain between the shoulder blades (OR 2.15, 95% CI 1.95-2.37), nausea or vomiting (OR 1.64, 95% CI 1.48-1.82) and shortness of breath (OR 1.34 (95% CI 1.21-1.48)).¹² Women with ACS had lower odds of sweating (OR 0.84, 95% CI 0.76-0.94) and presenting with chest pain (OR 0.70, 95% CI 0.63-0.78), but in both sexes chest pain remained the most common symptom (pooled prevalence men 79% and women 74%).¹² Importantly, researchers suggested standardization in methods of symptoms assessment is needed, because of the difficulties to formulate any definitive statements about symptom presentation, as studies assessed symptoms in different ways (questionnaires or abstracting from medical records).^{9,13-15} Abstracting symptom presentation from medical records may dilute symptom presentation, as they are translated by the clinician in medical terminology.¹⁶ Moreover, many studies suffer from recall or hindsight bias of both patient and researcher as they know the outcome (ACS).

For the clinician or telephone triage nurse it is crucial to differentiate ACS from other causes of chest discomfort. For that, studies are needed that include female and male patients presenting with chest discomfort, in which women and men who turn out to have ACS are compared to those who do not

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3 have ACS. Such studies are scarce. In a study performed among patients with chest discomfort seen at
4 the ED in the USA (77 women and 244 men with ACS, and 195 women and 240 men without ACS were
5 compared. Women with ACS more often reported arm pain than women without ACS (47% vs. 32%,
6 $p=0.021$), while men with ACS reported pressing feeling (63% vs. 54%, $p=0.035$) and chest pain (72% vs
7 60%, $p=0.005$) more often than men without ACS.¹³ In a recent Dutch OHS-PC study among 23 women
8 and 34 men with ACS, and 253 women and 208 men without ACS, differences in symptom presentation
9 between women and men were small.¹⁷ In men, radiation of pain (89.3% vs. 64.9%, $p\text{-value}=0.011$) was
10 discriminative for ACS, while stabbing chest pain (3.7% vs. 24.0%, $p\text{-value}=0.014$) was discriminative for
11 the absence of ACS. Both these symptoms were not discriminative in women (90.0% vs 78.6%, $p=0.227$,
12 and 15.8% vs. 18.8%, $p=0.743$), respectively.¹⁷

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21 We aimed to assess whether symptoms were different in patients with ACS from patients without ACS in
22 women and men separately. This, in the domain patients presenting with acute chest discomfort who
23 contact the OHS-PC. For analyses we used the very initial symptom presentation as available from the
24 recorded telephone triage conversations.

25 26 27 28 29 30 **Methods**

31 We performed a cross-sectional study with a random sample of 1,795 OHS-PC calls for chest discomfort
32 (chest pain, pressure, tightness, or discomfort) between 2014 and 2016.¹⁸ We first selected calls on the
33 basis of International Code for Primary Care (ICPC; a WHO world-wide code system for primary care)
34 codes (K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98) and keywords thoracic pain,
35 chest pain, myocardial infarction, heart attack and their common abbreviations mentioned by the triage
36 nurse in the electronic medical file at the OHS-PC.^{19,20} General practitioners who work at the OHS-PC
37 assign the ICPC codes to the call (see also appendix-table1). We combined ICPC-codes and keywords to
38 achieve a sample with a broad variety of symptoms to capture the entire domain of patients suspected
39 of ACS. We drew a random sample of all available calls of these patients with the Random Number
40 Generator (RAND) function in Microsoft Excel. Calls were excluded before re-listening when the
41 patients' age was below 18 years or when the patient did not live in the surrounding area of the OHS-
42 PCs (because then we could not retrieve a diagnosis from the general practitioner of these patients).
43 Calls were excluded during re-listening when it not concerned a triage call (e.g. inter-collegial
44 consultation) or when the recording was of poor quality (Figure 1). For a descriptive observational study,
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3 a method for sample size calculation is lacking. We therefore included a convenient number of patients,
4 that is, at least 80 patients with ACS in each sex category.
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8 We re-listened the telephone triage recordings and collected information about patient and
9 conversation characteristics, on symptom presentation, medical history, urgency allocation, and
10 involvement of a supervising general practitioner (GP) in the triage. Nine OHS-PC in the Netherlands
11 participated, serving a total population of 1.5 million people. The diagnosis was made after the phone
12 call, which was in the case of ACS nearly always done by the cardiologist (97.1%) in the hospital based
13 on (i) symptom presentation, (ii) levels of (high-sensitivity) troponin and (iii) electrocardiography results.
14 The final diagnoses were provided by the patients' GP, based on the electronic medical file including ED
15 and cardiologist discharge letters, and also the notes from the OHS-PC. We used medical information up
16 to 30-days following the contact with the OHS-PC, to allow us to include diagnoses of ACS that was
17 initially missed because the patient was not referred to the cardiologist the same day of the OHS-PC
18 contact. In none of the patients in the study we had evidence of a missed diagnosis of ACS.
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28 Context

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30 In the Netherlands, OHS-PC covers primary care during 73% of the week hours, and the initial contact is
31 by telephone. In most OHS-PC and EMS, the 'Netherlands Triage Standard' (NTS) is used as a decision
32 support to classify the urgency of the patients' conditions.²¹ Based on the patient's symptom
33 presentation, the triage nurse needs to choose the most appropriate complaint out of 56 'main
34 complaints'. Each NTS 'main complaint' incorporates a decision tree with hierarchically ordered
35 questions, which are similar for men and women. Triage nurses fill out the caller's responses in the
36 semi-automatic NTS system, which then generates urgency allocations linked to a timeframe within
37 which the patient should be seen by a physician or ambulance personnel (U0 (reanimation) to U5 (self-
38 care advice, see also appendix-table 2. The triage nurse can overrule this recommendation and up- or
39 downscale the urgency allocation, often after consulting the supervising GP.²² Since its introduction in
40 2011, the NTS system has, however, never been formally validated by correlating the generated
41 urgencies to clinical endpoints.²¹ All telephone calls to the OHS-PC are routinely recorded and archived
42 for five years for training and quality control purposes.
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53 Data analyses

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3 We compared patient and call characteristics between women with and without ACS, and men with and
4 without ACS. We analysed the association between urgency allocation and the final diagnosis ACS (with
5 or without other life threatening events (LTEs)). We considered pulmonary embolism, thoracic aortic
6 dissection and acute abdominal aneurysm as LTEs; patients with LTEs as well as those with ACS should
7 receive an U1-level urgency.
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13 For comparison of dichotomous variables we used the Chi² test or Fisher exact test and for continuous
14 variables the independent sample t-test or Mann-Whitney U test. Data analysis was performed using
15 SPSS, IBM version 25.
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19 20 Patient and public involvement

21 No patients were involved in setting the research question or the outcome measures, or in developing
22 plans for design, however, they were involved in the implementation of the study. In addition, they
23 were asked to advise on interpretation and writing up of results. Results will be shared and discussed
24 with the national patient community of cardiovascular diseases ('Harteraad').
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30 Ethics

31 The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics
32 Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the
33 Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to
34 subjects and could otherwise not be carried out logistically. Personal and research data were handled
35 and stored according to the European General Data Protection Regulation.
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41 **Results**

42 Among the 1,795 callers with chest discomfort (mean age 58.8 (SD 19.5) years, 55.3% women), 8.6% of
43 women and 15.0% of men had an ACS. In women with an ACS, 18.8% had a STEMI, 48.2% a NSTEMI,
44 20.0% an UAP, and 13.0% non-classified ACS. In men with ACS, 32.5% had a STEMI, 36.7% a NSTEMI,
45 27.5% an UAP, and 3.3% non-classified ACS.
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50 A total of 22 (2.2%) women and 23 men (2.9%) had another LTE than ACS (e.g. pulmonary embolism,
51 thoracic aortic dissection, acute abdominal aneurysm, acute heart failure).
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55 *Patient and call characteristics*

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3 In table 1, patient and call characteristics are presented for women and men with and without ACS.
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5 Men and women with ACS were older than those without ACS (mean age of women 73.6 vs. 57.8 years,
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7 $p<0.001$, men 67.2 vs. 56.9 years, $p<0.001$), and the mean duration of the telephone calls shorter
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9 (women 6:47 vs. 7:47 minutes, $p=0.021$, men 6:31 vs. 7:33 minutes, $p=0.004$). The GP was consulted for
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11 supervision by the triage nurse in the majority of cases (52.2% in women and 55.5% in men, $p=0.161$).
12
13 However, in women with ACS, the GP was less often consulted than in women without ACS (41.2% vs.
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15 53.2%, $p=0.034$). In men such a difference was not observed (53.3% vs. 55.9%, $p=0.607$).
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17 In around half of the calls, someone else called initially on behalf of the patient; somewhat less often in
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19 women than in men (49.5% vs. 54.7%, $p=0.029$). In cases with ACS, for both sexes more often someone
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21 else called than in those without ACS (in women 69.4% vs. 47.7%, $p<0.001$, in men 65.8% vs. 52.8%,
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23 $p=0.008$). In men with ACS, most often their female partner (53.3%) called, while in women with ACS, it
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25 was either their male partner (17.6%), their daughter (20.0%) or a nurse (17.6%). See appendix-table 3.
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27 Callers expressed concerns in nearly all calls, also in those without an ACS; women with ACS vs. women
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29 without ACS 97.3% vs. 88.9% ($p=0.109$), and men with ACS vs. men without ACS 96.3% vs. 86.5%
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31 ($p=0.041$).

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33 Both women and men with ACS had more often a history of coronary artery disease (women 42.5% vs.
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35 25.1%, $p=0.017$, and men 57.0% vs. 38.4%, $p=0.002$), but women with ACS had more often a history of
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37 diabetes (41.4% vs. 14.6%, $p<0.001$).

38 *Symptom presentation*

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40 Chest pain was the most common complaint, both in those with and without an ACS; in women with and
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42 without ACS 98.8% and 93.1% ($p=0.055$), and in men 92.4% and 94.5%, respectively ($p=0.364$).
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44 Retrosternal located chest pain was more common in women and men with ACS than in those without
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46 ACS (women 62.3% vs. 40.3%, $p=0.002$, and men 52.5% vs. 39.7%, $p=0.032$). Also, radiation of pain to
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48 the arms seemed indicative of ACS in both sexes (women with vs. without ACS 75.6% vs. 45.9%, $p<0.001$,
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50 and men 56.0% vs. 34.8%, $p<0.001$), as was pressing/heavy/tightening chest pain (women with vs.
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52 without ACS 78.6% vs. 61.5%, $p=0.011$ and men 82.1% vs. 57.4%, $p<0.001$). Only in women radiation to
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54 the jaw (50.0% vs. 22.9%, $p=0.007$) and severe pain (8 or more on a Numeric Rating Scale 0-10) was
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56 associated with ACS (65.4% vs. 38.1%, $p=0.006$). Only in men, stabbing pain was very rare in those with
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58 ACS (8.4% vs. 26.5%, $p<0.001$).

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3 Of the autonomous nervous system (ANS)-related symptoms, nausea/vomiting and dizziness/near
4 fainting were not associated with ACS in either sex, with the exception of a pale face that was in women
5 (50.0% vs. 29.8%, $p=0.017$), and sweating in men (52.4% vs. 38.1%, $p=0.015$).

8 Recognition of symptoms being similar to a previous cardiac event was associated with ACS in men
9 (52.9% vs. 32.1%, $p=0.004$), but not clearly for ACS in women (32.5% vs. 21.4%, $p=0.108$).

11 Subgroup analyses in 56 women and 58 men with diabetes showed that both women (85.7% vs. 58.3%,
12 $p<0.001$) and men with diabetes (67.2% vs. 51.5%, $p=0.033$) more often had shortness of breath than
13 those without diabetes, but as often chest discomfort (women 90.9% vs. 95.0%, $p=0.193$, men 89.2% vs
14 94.1%, $p=0.162$). Shortness of breath in patients with diabetes was not related to ACS diagnosis (women
15 81.8% vs. 86.7%, $p=0.680$, men 75.0% vs. 66.0%, $p=0.615$).

21 *Diagnoses*

23 Of the 205 patients with an ACS (85 women, 120 men), 55 (26.8%) patients had a STEMI (women 18.8%,
24 men 32.5%), 85 (41.5%) a NSTEMI (women 48.2%, men 36.7%), 50 (24.4%) unstable angina pectoris
25 (UAP) (women 20.0%, men 27.5%) and 15 (7.3%) unspecified ACS (women 13.0%, men 3.3%), the latter
26 also including two sudden cardiac deaths in women and one in men (Table 2). In nearly all cases (97.1%)
27 the ACS diagnosis was made by a cardiologist based on symptom presentation, troponin levels and
28 electrocardiography. Three patients died before arrival of the ambulance (they were classified as acute
29 cardiac death) and one patient died after resuscitation at the ED. Two patients were classified as ACS by
30 the GP; they were not referred to the hospital because of short life expectancy due to cancer.

32 There were 45 patients with other LTEs (2.5%) and the majority of patients had non-urgent medical
33 conditions (86.1%). The most common non-urgent diagnoses in both sexes were (i) non-urgent
34 cardiovascular diseases such as stable angina pectoris, stable heart failure and arrhythmias (19.5% of all
35 female callers with chest discomfort vs. 21.2% of male callers, $p=0.384$) and (ii) non-cardiac unspecified
36 chest pain (women 16.4% vs. 19.8% men, $p=0.061$). Women more often than men were diagnosed with
37 musculoskeletal problems (women 20.8% vs. men 14.1%, $p=0.001$) and psychogenic conditions (women
38 14.0% vs. men 8.4%, $p<0.001$). Of the patients who were diagnosed with a non-ACS diagnoses, 45.4%
39 were classified by a cardiologist, 5.5% by another hospital specialist (e.g. pulmonologist or internal
40 medicine specialist) and the remaining patients were diagnosed by a GP.

53 *Urgencies*

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3 Women and men with chest discomfort were equally sent an ambulance (43.6% vs. 46.6%, $p=0.200$).
4 This was also in women and men who had an ACS (72.9% vs. 70.0%, $p=0.647$), and in those with either
5 ACS or other LTEs (66.4% vs. 67.1%, $p=0.897$). See table 3.
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10 Discussion

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12 For both sexes, retrosternal pain, pain described as pressing, heavy or tightening, and radiation to the
13 arm were associated with ACS in patients who contacted the OHS-PC for chest discomfort. Radiation to
14 the jaw, severe pain, and a pale face was indicative for ACS in women. Sweating was positively
15 associated to ACS, and stabbing pain negatively associated to ACS in men with chest discomfort.
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17 Women and men with chest discomfort as also those with ACS were equally often sent an ambulance.
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22 Our finding that radiation of pain to the arm and retrosternal chest pain was discriminative for
23 diagnosing ACS in both sexes was also reported in a study among 2,475 patients with acute chest pain in
24 a multicentre ED-study.²³ Another ED-study among 1,334 patients with ACS showed that regardless of
25 ethnics status the most common presenting symptom was retrosternal pain/discomfort of any intensity.
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Our finding that radiation of pain to the arm and retrosternal chest pain was discriminative for
diagnosing ACS in both sexes was also reported in a study among 2,475 patients with acute chest pain in
a multicentre ED-study.²³ Another ED-study among 1,334 patients with ACS showed that regardless of
ethnics status the most common presenting symptom was retrosternal pain/discomfort of any intensity.
The aforementioned US study in the ED-setting reported that radiation to the arm was indicative for
ACS in women but not for men, and chest pressure was distinctive for men but not for women.¹³ The
only previously published OHS-PC study reported the opposite; radiation to the arm was associated with
ACS in men, but not in women. However, similar to our study, this study reported that stabbing pain was
very uncommon in men with ACS.¹⁷
In our study, women with ACS had more often a history of diabetes and were older than men with ACS,
which is in line with other studies.^{8,12} Some studies claim that patients with diabetes more often have
atypical symptoms of ACS, however a review of eight studies concluded the evidence of these studies
was conflicting.²⁵ We showed that both women and men with diabetes had more often shortness of
breath than those without diabetes, but shortness of breath in patients with diabetes was not helpful to
diagnose ACS. Regarding dispatching the ambulance, the aforementioned OHS-PC study and two EMS
studies showed, similar to our findings, that there was no difference in dispatch priorities between men
and women with ACS.^{4,17,26} This is in contrast with studies that show delay in hospital presentation of
women with ACS.^{9,27}

We need to realize that focusing on differences may blur the large overlap in symptoms. Moreover,
comparing *selectively* women with ACS to men with ACS as many previous studies did, is clinically

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3 irrelevant.^{9, 14, 28} Clinicians, including GPs, and triage nurses need to know whether and how women
4 with ACS differ from women without ACS, with the same question for men. Nevertheless, even
5 guidelines stick to comparing those with established disease, and express the view that women with ACS
6 more likely present with less specific symptoms than men with ACS.^{1, 29} Unfortunately, public awareness
7 campaigns follow this reasoning, and over-emphasize sex differences in women awareness campaigns
8 ('Go Red for Women' in the United States and 'Invisible me' in Australia).^{7, 28, 30} Unbalanced attention to
9 differences, neglecting the much larger overlap may even introduce new blind spots in recognizing ACS
10 in women.³¹

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18 A likely reason behind the predominant message that women present with other ACS symptoms than
19 men is the difference in pathophysiology of coronary artery disease. Women compared to men more
20 often have elongated plaques, located on bifurcations in epicardial coronaries, coronary spasm,
21 microvascular dysfunction, and spontaneous coronary dissection.^{30, 32} These pathophysiological
22 differences have an effect on interventional treatment and prognosis.^{2, 32} However, these differences
23 do not necessarily imply an effect on symptom presentation because the pain pathway is equal in
24 women and men: i.e. triggered by myocardial ischemia.^{33, 34} A supply and demand mismatch of the
25 myocardial oxygen consumption triggers sensory nerve endings in the myocardium and cause ischemia
26 symptoms, and this is irrespective of the fact whether the ischemia is caused by a plaque rupture in an
27 epicardial artery or spasm, or any other cause.³⁴ The sex differences in pathophysiology of ACS do
28 therefore not support the belief in differences in ACS symptoms between women and men.

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38 Another reason behind the belief of 'vague' symptom presentation in women with ACS might be that
39 they seem to present a larger number of symptoms than men with ACS, and this may be interpreted as
40 'vague' by physicians.^{15, 35} Presentation of multiple symptoms may influence the prompt recognition of
41 heart disease and initial actions on the part of health care providers.^{35, 36} In a study from 2018, 2009
42 women and 976 men hospitalized for myocardial infarction, healthcare providers initially thought
43 symptoms of women (53.4%) were less often heart-related than in men (36.7%).³⁵ Women and men had
44 the same chest pain symptoms, but women reported more additional symptoms.³⁵

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50 In our study, the call duration and the number of GP consultations by the triage nurse were similar
51 among women and men, suggesting that triage nurses seem not to experience more difficulties in
52 interpreting symptoms in women than men. This is in line with a prospective study with 2,795 patients
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3 with chest discomfort in ED-setting that showed the physicians' diagnostic uncertainty for the presence
4 of ACS in women was not more common as compared to men.³⁷

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6 Interestingly, in the majority of calls in our study someone else than the patient called the OHS-PC
7 (women with ACS 69.4%, without ACS 47.7%, and men with ACS 65.8%, and without ACS 52.8%). This
8 was also highlighted in an Australian study among 1,681 patients with an acute myocardial infarction; in
9 90.5% of the women with AMI someone else called on behalf of the patient and in 87.8% of the men
10 with AMI.³⁸ According to protocol in OHS-PC, triage nurses ask the patient to the phone, this to prevent
11 loss of (paralinguistic) information from the patient him/herself. In our study, in about 50% of the
12 conversations the patient took over the phone call.
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15 16 17 18 19 *Strengths and limitations*

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21 We could analyse the very initial conversation with symptom presentation of a large sample of patients
22 calling the OHS-PC because of chest discomfort. We analysed the conversations without knowledge of
23 the eventual diagnosis (no hindsight bias of the researcher or recall bias of the patient). Another
24 strength is that our results are generalizable to comparable primary care settings, e.g. UK and
25 Scandinavian countries, and possibly some other European countries.³ Our results may even be
26 generalizable to EMS settings, since the prior probability of having an ACS is comparable in EMS setting
27 as in OHS-PC settings.^{4 39}
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31 We had missing values on some clinical variables, a phenomenon common in routine care data. Future
32 research could focus on developing a multivariable prediction model useful with telephone triage to
33 estimate the risk of ACS in men and women suspected of ACS.
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41 **Conclusions**

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43 There were more similarities than differences in symptoms associated with the diagnosis ACS for
44 women and men. Important exceptions were severity, type, and radiation of pain, and in women a pale
45 face, and in men sweating.
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Data sharing statement

The data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution

FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DC conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript. DC, EdG, AH and RD contributed with and approved the final version of the manuscript.

References

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S and Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016;37:267-315.
2. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA and Eagle KA. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20-6.
3. Burman RA, Zakariassen E and Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice*. 2014;15:51.
4. Rawshani A, Larsson A, Gelang C, Lindqvist J, Gellerstedt M, Bang A and Herlitz J. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology*. 2014;176:859-65.
5. Mol KA, Smoczynska A, Rahel BM, Meeder JG, Janssen L, Doevendans PA and Cramer MJ. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart*. 2018;5:e000859.
6. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, Sullivan MD, DeLong ER, Bradley EH, Krumholz HM and Peterson ED. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. *Archives of internal medicine*. 2010;170:1834-41.
7. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J and Zaman S. Sex Differences Persist in Time to Presentation, Revascularization, and Mortality in Myocardial Infarction Treated With Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2019;8:e012161.
8. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G and Zheng ZJ. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama*. 2012;307:813-22.
9. Chen W, Woods SL and Puntillo KA. Gender differences in symptoms associated with acute myocardial infarction: a review of the research. *Heart Lung*. 2005;34:240-7.
10. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ and Long T. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Archives of internal medicine*. 2007;167:2405-13.
11. Sorensen NA, Neumann JT, Ojeda F, Schafer S, Magnussen C, Keller T, Lackner KJ, Zeller T, Karakas M, Munzel T, Blankenberg S, Westermann D and Schnabel RB. Relations of Sex to Diagnosis and Outcomes in Acute Coronary Syndrome. *J Am Heart Assoc*. 2018;7.
12. van Oosterhout REM, de Boer AR, Maas A, Rutten FH, Bots ML and Peters SAE. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc*. 2020;9:e014733.
13. Devon HA, Rosenfeld A, Steffen AD and Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *J Am Heart Assoc*. 2014;3:e000586.
14. Araujo C, Laszczynska O, Viana M, Melao F, Henriques A, Borges A, Severo M, Maciel MJ, Moreira I and Azevedo A. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. *BMJ open*. 2018;8:e018798.
15. Canto JG, Canto EA and Goldberg RJ. Time to standardize and broaden the criteria of acute coronary syndrome symptom presentations in women. *Can J Cardiol*. 2014;30:721-8.

16. Ferry AV, Anand A, Strachan FE, Mooney L, Stewart SD, Marshall L, Chapman AR, Lee KK, Jones S, Orme K, Shah ASV and Mills NL. Presenting Symptoms in Men and Women Diagnosed With Myocardial Infarction Using Sex-Specific Criteria. *J Am Heart Assoc.* 2019;8:e012307.
17. van der Meer MG, Appelman Y, Rutten KHG, van der Graaf Y, Nathoe HM, Doevendans PA, Smit M, Verheij E, Botermans A and Rutten FH. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open.* 2019;9:e031613.
18. Erkelens DC, Wouters LT, Zwart DL, Damoiseaux RA, De Groot E, Hoes AW and Rutten FH. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open.* 2019;9:e027477.
19. Soler JK, Okkes I, Wood M and Lamberts H. The coming of age of ICPC: celebrating the 21st birthday of the International Classification of Primary Care. *Family practice.* 2008;25:312-7.
20. Olagundoye OA, Malan Z, Mash B, van Boven K, Gusso G and Ogunnaike A. Reliability measurement and ICD-10 validation of ICPC-2 for coding/classification of diagnoses/health problems in an African primary care setting. *Family practice.* 2018;35:406-411.
21. van Ierland Y, van Veen M, Huibers L, Giesen P and Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Family practice.* 2011;28:334-41.
22. Keizer E, Maassen I, Smits M, Wensing M and Giesen P. Reducing the use of out-of-hours primary care services: A survey among Dutch general practitioners. *The European journal of general practice.* 2016;22:189-95.
23. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Wicki K, Zellweger C, Hoeller R, Moehring B, Sou SM, Mueller M, Denhaerynck K, Meller B, Stallone F, Henseler S, Bassetti S, Geigy N, Osswald S and Mueller C. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. *JAMA Intern Med.* 2014;174:241-9.
24. King-Shier K, Quan H, Kapral MK, Tsuyuki R, An L, Banerjee S, Southern DA and Khan N. Acute coronary syndromes presentations and care outcomes in white, South Asian and Chinese patients: a cohort study. *BMJ open.* 2019;9:e022479.
25. Stephen SA, Darney BG and Rosenfeld AG. Symptoms of acute coronary syndrome in women with diabetes: an integrative review of the literature. *Heart Lung.* 2008;37:179-89.
26. Herlitz J, Starke M, Hansson E, Ringvall E, Karlson BW and Waagstein L. Characteristics and outcome among women and men transported by ambulance due to symptoms arousing suspicion of acute coronary syndrome. *Med Sci Monit.* 2002;8:CR251-6.
27. Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, Zdravkovic M, Milicic D, Dilic M, Manfrini O, Koller A and Badimon L. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc.* 2017;6.
28. Diercks DB, Owen KP, Kontos MC, Blomkalns A, Chen AY, Miller C, Wiviott S and Peterson ED. Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (NCDR ACTION Registry-GWTG). *American heart journal.* 2010;160:80-87 e3.
29. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on Quality of C and Outcomes R. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. *Circulation.* 2016;133:916-47.
30. Khamis RY, Ammari T and Mikhail GW. Gender differences in coronary heart disease. *Heart.* 2016;102:1142-9.

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3 31. Amalberti R. *Navigating safety: necessary compromises and trade-offs – theory and practice*. Heidelberg: Springer; 2013.
- 4
5 32. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas
6 AHEM, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V,
7 EUGenMed and Grp CCS. Gender in cardiovascular diseases: impact on clinical manifestations,
8 management, and outcomes. *European heart journal*. 2016;37:24-+.
- 9
10 33. Leach A and Fisher M. Myocardial ischaemia and cardiac pain - a mysterious relationship. *Br J*
11 *Pain*. 2013;7:23-30.
- 12 34. Rosen SD. From heart to brain: the genesis and processing of cardiac pain. *Can J Cardiol*.
13 2012;28:S7-19.
- 14 35. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA
15 and D'Onofrio G. Sex Differences in the Presentation and Perception of Symptoms Among Young
16 Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of
17 Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137:781-790.
- 18 36. Goldberg R, Goff D, Cooper L, Luepker R, Zapka J, Bittner V, Osganian S, Lessard D, Cornell C,
19 Meshack A, Mann C, Gilliland J and Feldman H. Age and sex differences in presentation of symptoms
20 among patients with acute coronary disease: the REACT Trial. Rapid Early Action for Coronary
21 Treatment. *Coron Artery Dis*. 2000;11:399-407.
- 22 37. Hillinger P, Twerenbold R, Wildi K, Rubini Gimenez M, Jaeger C, Boeddinghaus J, Nestelberger T,
23 Grimm K, Reichlin T, Stallone F, Puelacher C, Sabti Z, Kozhuharov N, Honegger U, Ballarino P, Miro O,
24 Denhaerynck K, Ekrem T, Kohler C, Bingisser R, Osswald S and Mueller C. Gender-specific uncertainties in
25 the diagnosis of acute coronary syndrome. *Clin Res Cardiol*. 2017;106:28-37.
- 26 38. Coventry LL, Bremner AP, Jacobs IG and Finn J. Myocardial infarction: sex differences in
27 symptoms reported to emergency dispatch. *Prehosp Emerg Care*. 2013;17:193-202.
- 28 39. Deakin CD, Sherwood DM, Smith A and Cassidy M. Does telephone triage of emergency (999)
29 calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call
30 prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657
31 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency medicine journal : EMJ*.
32 2006;23:232-5.
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Figure 1. Flowchart study population.

Table 1. Baseline characteristics of 993 (55.3%) women and 802 (44.7%) men patients contacting the OHS-PC with chest discomfort (pain, pressure, tightness, or discomfort)

Characteristics	993 women			802 men		
	ACS N = 85 (8.6%)	No ACS N = 908 (91.4%)	p-value	ACS N = 120 (15.0%)	No ACS N = 682 (85.0%)	p-value
Mean age in years (SD)	73.6 (±14.1)	57.8 (±20.1)	<0.001	67.2 (±13.0)	56.9 (±19.2)	<0.001
Call characteristics						
Mean call duration in min (SD)	6:47 (±5:16)	7:47 (±3:48)	0.021	6:31 (±3:13)	7:33 (±3:42)	0.004
Mean patient's introduction duration in min (SD)	0:14 (± 0:08)	0:19 (±0:13)	<0.001	0:16 (±0:11)	0:19 (±0:14)	0.060
Triage nurse consulted the GP	35 (41.2)	483 (53.2)	0.034	64 (53.3)	381 (55.9)	0.607
Someone else called on behalf of patient	59 (69.4)	433 (47.7)	<0.001	79 (65.8)	360 (52.8)	0.008
The patient or person who called expressed concerned (n=922)	36 (97.3)	409 (88.9)	0.109	52 (96.3)	321 (86.5)	0.041
Chest pain (n=1739)	81 (98.8)	817 (93.1)	0.055	110 (92.4)	624 (94.5)	0.364
Severe Pain (>7 on a scale 0-10) (n=753)	17 (65.4)	147 (38.1)	0.006	13 (23.6)	87 (30.4)	0.312
Duration						
> 15 min (n=1501)	66 (100)	729 (95.8)	0.102	99 (97.1)	541 (94.6)	0.292
< 12 hrs (n=1563)	60 (85.7)	575 (72.7)	0.018	88 (81.5)	431 (72.6)	0.052
Location (n=1267)*						
Retrosternal	33 (62.3)	263 (40.3)	0.002	42 (52.5)	191 (39.7)	0.032
Right or left side thorax	14 (26.4)	260 (39.8)	0.054	26 (32.5)	211 (43.9)	0.057
Type of pain (n=1334)**						
Pressing/heavy/tightening	44 (78.6)	423 (61.5)	0.011	78 (82.1)	284 (57.4)	<0.001

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3 Stabbing	8 (14.3)	155 (22.5)	0.152	8 (8.4)	131 (26.5)	<0.001
4						
5 Radiation of chest pain (n=1391) ***						
6						
7 Any location	61 (85.9)	485 (68.6)	0.002	65 (63.7)	292 (57.1)	0.218
8						
9 Arm	31 (75.6)	188 (45.9)	<0.001	47 (56.0)	117 (34.8)	<0.001
10						
11 Between the shoulder blades	11 (52.4)	159 (41.7)	0.336	14 (27.5)	91 (29.4)	0.781
12						
13 Jaws	10 (50.0)	66 (22.9)	0.007	1 (2.6)	28 (11.6)	0.146
14						
15 Shortness of breath (n=1365)	47 (72.3)	455 (66.3)	0.328	53 (60.9)	329 (62.4)	0.788
16						
17 Symptoms similar to previous cardiac	13 (32.5)	79 (21.4)	0.108	27 (52.9)	92 (32.1)	0.004
18 events (n=748)						
19						
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21 ANS-related symptoms						
22						
23 Sweating (n=1130)	28 (49.1)	234 (42.5)	0.340	43 (52.4)	168 (38.1)	0.015
24						
25 Nausea or vomiting (n=808)	16 (44.4)	240 (56.2)	0.173	27 (45.8)	122 (42.7)	0.661
26						
27 Pallor (n=634)	17 (50.0)	91 (29.8)	0.017	20 (40.8)	82 (33.)	0.315
28						
29 Dizziness or near fainting n=1599)	13 (18.6)	197 (24.4)	0.277	17 (15.9)	127 (20.2)	0.249
30						
31 Medical history						
32						
33 CV disease or risk factors (n=1461)	54 (78.3)	407 (57.5)	0.001	75 (72.1)	359 (61.9)	0.046
34						
35 Coronary artery disease (n=966)	17 (42.5)	114 (25.1)	0.017	45 (57.0)	151 (38.4)	0.002
36						
37 Hypertension (n=756)	22 (71.0)	142 (35.1)	<0.001	17 (47.2)	94 (33.0)	0.091
38						
39 Diabetes mellitus (n=745)	12 (41.4)	56 (14.6)	<0.001	12 (28.6)	59 (20.3)	0.220
40						
41 Hypercholesterolemia or use of statins	8 (36.4)	81 (23.2)	0.161	19 (45.2)	62 (23.3)	0.003
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43 (n=679)						
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46 *P-value comparing retrosternal or left/right side thorax vs. others locations of pain together (rethroasternal, left/right side thorax,
47 back/shoulder, epigastric region)

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49 * Pressing/ heavy/tightening pain vs. other types of pain (stabbing, burning, cramping, tearing). Stabbing pain: stabbing vs. other types of
50 pain (pressing/heavy/tightening, burning, cramping, tearing)

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52 *** P-value comparing radiation arm or back/shoulder or jaws vs. no radiation

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54 NRS: Numeric Rating Scale

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ANS-related symptoms: Autonomous nervous system related symptoms
CV disease or risk factors; a history of previous coronary artery disease, heart failure, stroke, cardiac arrhythmia, hypertension, and/or diabetes (patient reported)
Coronary artery disease: History of prior MI, PCI, CABG, stable or unstable angina pectoris (patient reported)

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Table 2. Diagnosis of 1,795 patients who contacted the OHS-PC for chest discomfort (pain, pressure, tightness, or discomfort), divided in women and men

	Women n= 993 (55.3%)	Men n=802 (44.7%)	p-value
Acute coronary syndrome	85 (8.6)	120 (15.0)	<0.001
STEMI	16 (18.8)	39 (32.5)	0.037
NSTEMI	41 (48.2)	44 (36.7)	0.114
UAP	17 (20.0)	33 (27.5)	0.250
Non-classified ACS	11 (13.0)	4 (3.3)	0.013
Life threatening events (LTE's)	22 (2.2)	23 (2.9)	0.448
Pulmonary embolism	6 (27.3)	7 (30.4)	0.815
Thoracic aortic dissection	4 (18.2)	2 (8.7)	0.349
Acute abdominal aneurysm	3 (13.6)	2 (8.7)	0.598
Other*	9 (40.9)	12 (52.2)	0.449
Non-urgent cardiovascular diseases**	194 (19.5)	170 (21.2)	0.384
Non-cardiac chest pain, not further specified ***	163 (16.4)	159 (19.8)	0.061
Musculoskeletal pain	199 (20.0)	113 (14.1)	0.001
Psychogenic disorders	139 (14.0)	67 (8.4)	<0.001
Gastrointestinal tract disorders	76 (7.7)	62 (7.7)	0.951
Respiratory tract disorders	52 (5.2)	45 (5.6)	0.727
Other non-urgent diagnoses***	63 (6.3)	43 (5.4)	0.380
<p>*Acute heart failure, stroke, severe COPD exacerbation, sepsis, coronary spasm probably caused by hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.</p> <p>** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension</p>			

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*** Cardiac pathology unlikely after cardiologist’s diagnostic work-up, but without differential diagnosis

**** Amongst others: anaemia, malignancy, vasovagal collapse, side effects medication, dermatologic diseases

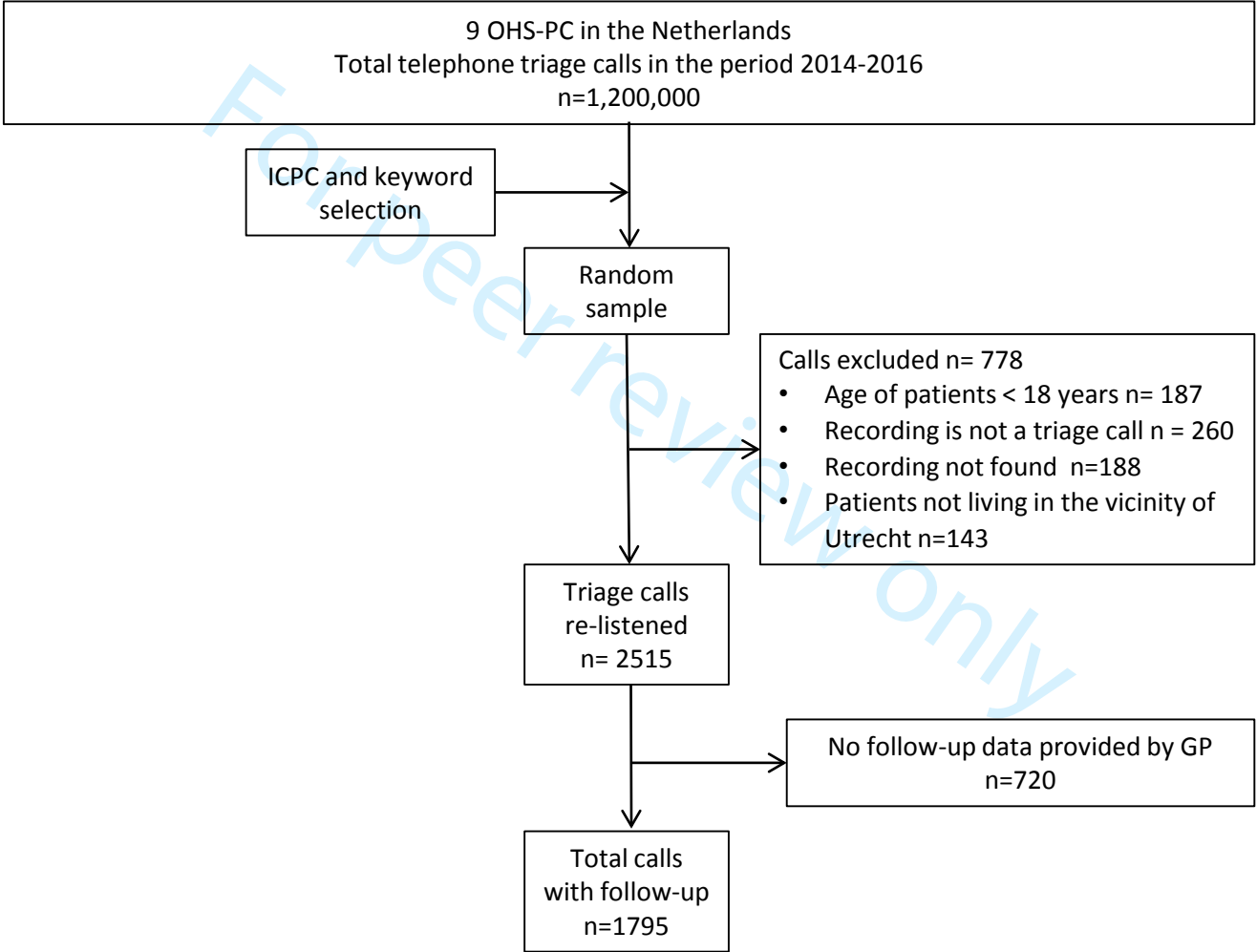
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Table 3. Association between urgency allocation, diagnose ACS and other life threatening events (LTE)

Women	ACS n=85 (8.6%)	No ACS n=908 (91.4%)	p-value 1*	p-value 2**
U1	62 (72.9)	371 (40.9)	<0.001	<0.001
U2	12 (14.1)	231 (25.4)		
U3-U5	11 (13.0)	306 (33.6)		
Men	ACS n=120 (15.0%)	No ACS n=682 (85.0%)		
U1	84 (70.0)	290 (42.5)	<0.001	<0.001
U2	19 (15.8)	142 (20.8)		
U3-U5	17 (14.2)	250 (36.7)		
Women	ACS or LTE n=107 (10.8%)	No ACS or LTE n=886 (89.2%)		
U1	71 (66.4)	362 (40.9)	<0.001	<0.001
U2	21 (19.6)	222 (25.1)		
U3-U5	15 (14.0)	302 (34.0)		
Men	ACS or LTE n=143 (17.8%)	No ACS or LTE n=659 (82.2%)		
U1	96 (67.1)	278 (42.2)	<0.001	<0.001
U2	24 (16.8)	137 (20.8)		
U3-U5	23 (16.1)	244 (37.0)		
<p>* P-value 1: U1 vs. U2, U3, U4 and U5</p> <p>** P-value 2: U1,U2 vs. U3,U4,U5</p> <p>***LTE = life threatening event. Life threatening events consist of: ACS; pulmonary embolism; thoracic aortic dissection; acute heart failure; stroke; abdominal aortic aneurysm; severe COPD exacerbation; diabetic ketoacidosis; coronary spasm probably caused by hypokalaemia; epileptic insult; bleeding from oesophageal varices; ovarian torsion; ventricular fibrillation.</p>				

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Figure 1. Flowchart study population



Supplementary file

Appendix-Table 1: Overview of ICPC-codes used to select calls

ICPC code	Calls of patients with ACS N=205 (%)	Calls of patients without ACS N=1,590 (%)
K01 Pain attributed to the heart	112 (54.6)	485 (30.5)
K02 Pressure/tightness attributed to the heart	39 (19.0)	184 (11.6)
K03 Other cardiovascular pain	1 (0.5)	6 (0.4)
K24 Fear of heart attack	1 (0.5)	8 (0.5)
K74 Angina pectoris	19 (9.3)	101 (6.4)
K75 Acute myocardial infarction	7 (3.4)	22 (1.4)
K76 Other/chronic ischaemic heart disease	0 (0.0)	2 (0.1)
K77 Heart failure	0 (0.0)	11 (0.7)
K93 Pulmonary embolism	0 (0.0)	15 (0.9)
L04 Chest discomfort	25 (12.2)	689 (43.9)
P74 Anxiety disorder	0 (0.0)	12 (0.8)
R02 Shortness of breath	1 (0.5)	36 (2.3)
R98 Hyperventilation	0 (0.0)	10 (0.6)

Appendix-Table 2: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advice given by triage nurse

Appendix-Table 3: Relation of caller to patient in women and men with ACS

	Women n= 85 (8.6%)	Men n = 120 (15.0%)	P-value
Someone else calls on behalf of patient	59 (69.4)	79 (65.8)	0.590
Partner	16 (18.8)	64 (53.3)	<0.001
Son, daughter or other family member	20 (23.5)	8 (6.7)	0.001
Nurse	15 (17.6)	4 (3.3)	<0.001
Other (neighbour, friend, colleague)	8 (9.4)	3 (2.5)	0.030
Patient takes over the phone call on request of the triage nurse	27 (45.8)	58 (73.4)	<0.001

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
/Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8

		(b) Report category boundaries when continuous variables were categorized	7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study

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3 **Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage:**
4 **a cross-sectional study**
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14 All authors have completed the Unified Competing Interest form and declare no support from any
15 organization for the submitted work; no financial relationships with any organizations that might have
16 an interest in the submitted work in the previous three years, no other relationships or activities that
17 could appear to have influenced the submitted work.
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23 **Transparency declaration**

24 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and
25 transparent account of the study being reported; that no important aspects of the study have been
26 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been
27 explained.
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Abstract

Objectives To identify clinical variables that are associated with the diagnosis acute coronary syndrome (ACS) in women and men with chest discomfort who contact out-of-hours primary care (OHS-PC) by telephone, and to explore whether there are indications whether these variables differ among women and men.

Design Cross-sectional study in which we compared patient and call characteristics of triage call recordings between women with and without ACS, and men with and without ACS.

Setting Nine OHS-PC in the Netherlands.

Participants 993 women and 802 men who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2016.

Primary outcome measure Diagnosis of ACS retrieved from the patient's medical record in general practice, including hospital specialists' discharge letters.

Results Among 1,795 patients (mean age 58.8 (SD 19.5) years, 55.3% women), 15.0% of men and 8.6% of women had an ACS. In both sexes, retrosternal chest pain was associated with ACS (women with ACS vs. without 62.3% vs. 40.3%, $p=0.002$, men with ACS vs. without 52.5% vs. 39.7%, $p=0.032$, gender interaction $p=0.323$), as was pressing/heavy/tightening pain (women 78.6% vs. 61.5%, $p=0.011$, men 82.1% vs. 57.4%, $p<0.001$, gender interaction $p=0.368$) and radiation to the arm (women 75.6% vs. 45.9%, $p<0.001$, men 56.0% vs. 34.8%, $p<0.001$, gender interaction $p=0.339$). Results indicate that only in women, severe pain (65.4% vs. 38.1%, $p=0.006$, gender interaction $p=0.007$) and radiation to jaw (50.0% vs. 22.9%, $p=0.007$, gender interaction $p=0.015$) were associated with ACS. Ambulances were dispatched equally in women (72.9%) and men with ACS (70.0%).

Conclusion Our results indicate there were more similarities than differences in symptoms associated with the diagnosis ACS for women and men. Important exceptions were severity and radiation of pain in women. Whether these differences have an impact on predicting ACS needs to be further investigated with multivariable analyses.

Trial number: NTR7331

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3 **Keywords (5): acute coronary syndrome, gender, primary care, telephone triage, chest discomfort**
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7 **Strengths and limitations of this study**
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- 10 • We could analyse the very initial conversation with symptom presentation of a large sample of
11 patients calling for acute chest discomfort, without the risk of hindsight bias of the researcher or
12 recall bias of the patient.
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 - 14 • We analysed clinical variables associated with ACS in gender subgroup analyses and across
15 gender with statistical interaction terms.
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 - 17 • Results are generalizable to comparable primary care settings in the United Kingdom and
18 Scandinavian Countries, and our results may even be generalizable to emergency medical
19 service (EMS, '112' or '911') settings.
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 - 21 • For the purpose of improving telephone triage interviewing, prediction rule development with
22 multivariable regression analysis is needed.
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Introduction

Adequate triage and early diagnosis is key in patients with acute chest discomfort because they might have an acute coronary syndrome (ACS) for which lifesaving early interventions are available. ACS is an umbrella term including ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).¹ For the diagnosis of ACS an abnormal electrocardiogram (ST and/or T wave abnormalities) and/or elevated blood levels of troponin I or T are needed. ACS may then be further subdivided into ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) if the troponin levels are elevated.¹ If troponin levels are not elevated (or increased over time), it is called unstable angina pectoris (UAP).¹ Increased preventive measures and development of (timely) effective therapeutic interventions ('time is muscle') have resulted in improved outcomes and prognosis in ACS.² Telephone triage of patients with chest discomfort, as done in out-of-hours service primary care (OHS-PC) and emergency medical services (EMS or ambulance dispatch centres) is, however, challenging because it is difficult to differentiate ACS from other causes of chest discomfort based on symptoms only.^{3,4} Importantly, the majority of patients with chest discomfort (80%) in the Netherlands first approach the general practitioner (GP) or OHS-PC, and 20% directly calls the ambulance (112) or are self-referrals to the emergency department (ED).⁵

Previous hospital-based studies reported a delayed recognition of ACS in women compared to men.^{6,7} It was suggested that this delayed recognition was related to a less specific presentation in women.^{8,9} This caused an ongoing debate on whether women with ACS compared to men present with less specific symptoms, and how this affects diagnosis, but also treatment, and prognosis.^{10,11} A recent meta-analysis of 27 studies showed that women with ACS compared to men with ACS had higher odds of presenting with pain between the shoulder blades (OR 2.15, 95% CI 1.95-2.37), nausea or vomiting (OR 1.64, 95% CI 1.48-1.82) and shortness of breath (OR 1.34 (95% CI 1.21-1.48)).¹² Women with ACS had lower odds of sweating (OR 0.84, 95% CI 0.76-0.94) and presenting with chest pain (OR 0.70, 95% CI 0.63-0.78), but in both sexes chest pain remained the most common symptom (pooled prevalence men 79% and women 74%).¹² Importantly, researchers suggested standardization in methods of symptoms assessment is needed, because of the difficulties to formulate any definitive statements about symptom presentation, as studies assessed symptoms in different ways (questionnaires or abstracting from medical records).^{9,13-15} Abstracting symptom presentation from medical records may dilute symptom presentation, as they are translated by the clinician in medical terminology.¹⁶ Moreover, many studies suffer from recall or hindsight bias of both patient and researcher as they know the outcome (ACS).

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5 For the clinician or telephone triage nurse it is crucial to differentiate ACS from other causes of chest
6 discomfort. For that, studies are needed that include female and male patients presenting with chest
7 discomfort, in which women and men who turn out to have ACS are compared to those who do not
8 have ACS. Such studies are scarce. In a study performed among patients with chest discomfort seen at
9 the ED in the USA (77 women and 244 men with ACS, and 195 women and 240 men without ACS were
10 compared.¹³ Women with ACS more often reported arm pain than women without ACS (47% vs. 32%,
11 $p=0.021$), while men with ACS reported pressing feeling (63% vs. 54%, $p=0.035$) and chest pain (72% vs
12 60%, $p=0.005$) more often than men without ACS.¹³ In a recent Dutch OHS-PC study among 23 women
13 and 34 men with ACS, and 253 women and 208 men without ACS, symptoms associated with ACS in
14 women and men seemed quite similar and the authors conclude that discriminating ACS in patients with
15 chest discomfort who contacted primary care OHS is difficult in both women and men.¹⁷

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20 We aimed to identify clinical variables that are associated with the diagnosis ACS in women and men
21 with chest discomfort who contact out-of-hours primary care (OHS-PC) by telephone, and to explore
22 whether there are indications these variables differ among women and men. For analyses we used the
23 very initial symptom presentation as available from the recorded telephone triage conversations.

24 25 26 27 28 29 30 31 32 33 34 **Methods**

35 We performed a cross-sectional diagnostic factor study with a random sample of 1,795 OHS-PC calls for
36 chest discomfort (chest pain, pressure, tightness, or discomfort) between 2014 and 2016.^{18,19} We first
37 selected calls on the basis of International Code for Primary Care (ICPC; a WHO world-wide code system
38 for primary care) codes (K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98, appendix-table
39 1) and keywords thoracic pain, chest pain, myocardial infarction, heart attack and their common
40 abbreviations mentioned by the triage nurse in the electronic medical file (EMF) at the OHS-PC.^{20,21}
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42 General practitioners who work at the OHS-PC assign the ICPC codes to the call. We combined ICPC-
43 codes and keywords to achieve a sample with a broad variety of symptoms to capture the entire domain
44 of patients suspected of ACS. We listed all available calls of these patients and assigned random
45 numbers with the Random Number Generator (RAND) function in Microsoft Excel to retrieve a random
46 sample. Calls were excluded before re-listening when the patients' age was below 18 years or when the
47 patient did not live in the surrounding area of the OHS-PCs (because then we could not retrieve a
48 diagnosis from the general practitioner of these patients). Calls were excluded during re-listening when
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3 it not concerned a triage call (e.g. inter-collegial consultation) or when the recording was of poor quality
4 (Figure 1). Adequate methods for sample calculation of a diagnostic factor study is yet lacking. We
5 therefore included a convenient number of patients, that was, at least 80 patients with ACS in each sex
6 category. This number was chosen primarily based for practical and feasibility reasons.
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11 We re-listened the telephone triage recordings to collect information about patient and conversation
12 characteristics, on symptom presentation, medical history, urgency allocation, and involvement of a
13 supervising general practitioner (GP) in the triage conversation. Gender considered the self-identified
14 gender of the patient. Call duration and age were retrieved from the electronic EMF of the OHS-PC. Nine
15 OHS-PC in the Netherlands participated, serving a total population of 1.5 million people. The diagnosis
16 was made after the phone call, which was in the case of ACS nearly always done by the cardiologist
17 (97.1%) in the hospital based on (i) symptom presentation, (i) levels of (high-sensitivity) troponin and (iii)
18 electrocardiography results. The final diagnoses were provided by the patients' GP, based on the
19 electronic medical file including ED and cardiologist discharge letters, and also the notes from the OHS-
20 PC. We used medical information up to 30-days following the contact with the OHS-PC, to allow us to
21 include diagnoses of ACS that was initially missed because the patient was not referred to the
22 cardiologist the same day of the OHS-PC contact. In none of the patients in the study we had evidence of
23 a missed diagnosis of ACS.
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34 35 Context

36 In the Netherlands, OHS-PC covers primary care during 73% of the week hours, and the initial contact is
37 by telephone. In most OHS-PC and EMS, the 'Netherlands Triage Standard' (NTS) is used as a decision
38 support to classify the urgency of the patients' conditions.²² Based on the patient's symptom
39 presentation, the triage nurse needs to choose the most appropriate complaint out of 56 'main
40 complaints'. Each NTS 'main complaint' incorporates a decision tree with hierarchically ordered
41 questions, which are similar for men and women. Triage nurses fill out the caller's responses in the
42 semi-automatic NTS system, which then generates urgency allocations linked to a timeframe within
43 which the patient should be seen by a physician or ambulance personnel (U0 (reanimation) to U5 (self-
44 care advice) appendix-table 2). The triage nurse can overrule this recommendation and up- or
45 downscale the urgency allocation, often after consulting the supervising GP.²³ A recent validation study
46 showed that the diagnostic accuracy of the NTS for patients with chest discomfort is poor (sensitivity
47 0.73 (95% CI 0.68-0.78) and specificity 0.43 (95% CI 0.40-0.45)), as calculated on the outcome ACS or
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3 other life-threatening events (LTEs).²⁴ All telephone calls to the OHS-PC are routinely recorded and
4 archived for five years for training and quality control purposes.
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8 Data analyses

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10 We compared patient and call characteristics between women with and without ACS, and men with and
11 without ACS. For comparison of dichotomous variables we used the Chi² test or Fisher exact test and for
12 continuous variables the independent sample t-test or Mann-Whitney U test. We performed interaction
13 analysis across gender separately for each clinical variable with logistic regression analyses, to explore
14 whether there are indications that these variables are differently associated with the diagnosis ACS
15 among men and women. We analysed the association between urgency allocation and the final
16 diagnosis ACS (alone or including other LTEs) with the Chi² test. We considered pulmonary embolism,
17 thoracic aortic dissection and acute abdominal aneurysm as LTEs; patients with LTEs as well as those
18 with ACS should receive an U1-level urgency.
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20 Data analysis was performed using SPSS, IBM version 25.
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25 Patient and public involvement

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28 No patients were involved in setting the research question or the outcome measures, or in developing
29 plans for design, however, they were involved in the implementation of the study. In addition, they
30 were asked to advise on interpretation and writing up of results. Results will be shared and discussed
31 with the national patient community of cardiovascular diseases ('Harteraad').
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38 Ethics

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40 The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics
41 Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the
42 Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to
43 subjects and could otherwise not be carried out logistically. Personal and research data were handled
44 and stored according to the European General Data Protection Regulation.
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50 **Results**

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52 Among the 1,795 callers with chest discomfort (mean age 58.8 (SD 19.5) years, 55.3% women), 8.6% of
53 women and 15.0% of men had an ACS. In women with an ACS, 18.8% had a STEMI, 48.2% a NSTEMI,
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20.0% an UAP, and 13.0% non-classified ACS. In men with ACS, 32.5% had a STEMI, 36.7% a NSTEMI, 27.5% an UAP, and 3.3% non-classified ACS.

A total of 22 (2.2%) women and 23 men (2.9%) had another LTE than ACS (e.g. pulmonary embolism, thoracic aortic dissection, acute abdominal aneurysm, acute heart failure).

Patient and call characteristics

Men and women with ACS were older than those without ACS (mean age of women with ACS 73.6 vs. without ACS 57.8 years, $p<0.001$, men 67.2 vs. 56.9 years, $p<0.001$, gender interaction $p=0.094$), and the mean duration of the telephone calls was shorter (women 6:47 vs. 7:47 minutes, $p=0.021$, men 6:31 vs. 7:33 minutes, $p=0.004$, gender interaction $p=0.803$) (table 1). The GP was consulted for supervision by the triage nurse in the majority of cases (52.2% in women and 55.5% in men). However, in women with ACS, the GP was less often consulted than in women without ACS (41.2% vs. 53.2%, $p=0.034$), but in men such a difference was not observed (53.3% vs. 55.9%, $p=0.607$, gender interaction $p=0.208$).

In around half of the calls, someone else called initially on behalf of the patient (49.5% in women vs. 54.7% in men). In cases with ACS, for both sexes more often someone else called than in those without ACS (in women 69.4% vs. 47.7%, $p<0.001$, in men 65.8% vs. 52.8%, $p=0.008$, gender interaction $p=0.251$). In men with ACS, most often their female partner (53.3%) called, while in women with ACS, it was either their male partner (17.6%), their daughter (20.0%) or a nurse (17.6%) (appendix-table 3). Callers expressed concerns in nearly all calls, also in those without an ACS; women with ACS vs. women without ACS 97.3% vs. 88.9% ($p=0.109$), and men with ACS vs. men without ACS 96.3% vs. 86.5% ($p=0.041$) (gender interaction $p=0.935$).

Both women and men with ACS had more often a history of coronary artery disease (women 42.5% vs. 25.1%, $p=0.017$, and men 57.0% vs. 38.4%, $p=0.002$, gender interaction $p=0.927$), but women with ACS had more often a history of diabetes (41.4% vs. 14.6%, $p<0.001$, gender interaction $p=0.079$).

Symptom presentation

Chest pain was the most common complaint, both in patients with and without an ACS (women with ACS and without 98.8% and 93.1%, $p=0.055$, in men 92.4% and 94.5%, $p=0.364$, gender interaction $p=0.048$). Retrosternal located chest pain was more common in women and men with ACS than in those without ACS (women 62.3% vs. 40.3%, $p=0.002$, and men 52.5% vs. 39.7%, $p=0.032$, gender interaction $p=0.323$). Also, radiation of pain to the arms was associated with ACS in both sexes (women with vs.

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3 without ACS 75.6% vs. 45.9%, $p < 0.001$, and men 56.0% vs. 34.8%, $p < 0.001$, gender interaction $p = 0.339$,
4 as was pressing/heavy/tightening chest pain (women with vs. without ACS 78.6% vs. 61.5%, $p = 0.011$ and
5 men 82.1% vs. 57.4%, $p < 0.001$, gender interaction $p = 0.368$). Only in women radiation to the jaw
6 (50.0% vs. 22.9%, $p = 0.007$, gender interaction $p = 0.015$) and severe pain (8 or more on a Numeric Rating
7 Scale 0-10) was associated with ACS (65.4% vs. 38.1, $p = 0.006$, gender interaction $p = 0.007$). Only in men,
8 stabbing pain was very rare in those with ACS (8.4% vs. 26.5%, $p < 0.001$, gender interaction $p = 0.141$).
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10 Of the autonomous nervous system (ANS)-related symptoms, nausea/vomiting and dizziness/near
11 fainting were not associated with ACS in either sex, with the exception of a pale or ashen face that was
12 in women (55.6% vs. 35.5%, $p = 0.019$, gender interaction $p = 0.545$), and sweating in men (52.4% vs.
13 38.1%, $p = 0.015$, gender interaction $p = 0.418$). Recognition of symptoms being similar to a previous
14 cardiac event was associated with ACS in men (52.9% vs. 32.1%, $p = 0.004$), but not clearly for ACS in
15 women (32.5% vs. 21.4%, $p = 0.108$, gender interaction $p = 0.532$).
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25 Subgroup analyses in 56 women and 58 men with diabetes showed that both women (85.7% vs. 58.3%,
26 $p < 0.001$) and men with diabetes (67.2% vs. 51.5%, $p = 0.033$, gender interaction $p = 0.119$) more often had
27 shortness of breath than those without diabetes, but as often chest discomfort (women 90.9% vs.
28 95.0%, $p = 0.193$, men 89.2% vs 94.1%, $p = 0.162$, gender interaction $p = 0.969$). Shortness of breath in
29 patients with diabetes was not related to ACS diagnosis (women 81.8% vs. 86.7%, $p = 0.680$, men 75.0%
30 vs. 66.0%, $p = 0.615$, gender interaction $p = 0.520$).
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37 *Diagnoses*

38 Of the 205 patients with an ACS (85 women, 120 men), 55 (26.8%) patients had a STEMI (women 18.8%,
39 men 32.5%), 85 (41.5%) a NSTEMI (women 48.2%, men 36.7%), 50 (24.4%) unstable angina pectoris
40 (UAP) (women 20.0%, men 27.5%) and 15 (7.3%) unspecified ACS (women 13.0%, men 3.3%), the latter
41 also including two sudden cardiac deaths in women and one in men (Table 2). In nearly all cases (97.1%)
42 the ACS diagnosis was made by a cardiologist based on symptom presentation, troponin levels and
43 electrocardiography. Three patients died before arrival of the ambulance (they were classified as acute
44 cardiac death) and one patient died after resuscitation at the ED. Two patients were classified as ACS by
45 the GP; they were not referred to the hospital because of short life expectancy due to cancer.
46
47 There were 45 patients with other LTEs (2.5%) and the majority of patients had non-urgent medical
48 conditions (86.1%). The most common non-urgent diagnoses in both sexes were (i) non-urgent
49 cardiovascular diseases such as stable angina pectoris, stable heart failure and arrhythmias (19.5% of all
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3 female callers with chest discomfort vs. 21.2% of male callers, $p=0.384$) and (ii) non-cardiac unspecified
4 chest pain (women 16.4% vs. 19.8% men, $p=0.061$). Women more often than men were diagnosed with
5 musculoskeletal problems (women 20.8% vs. men 14.1%, $p=0.001$) and psychogenic conditions (women
6 14.0% vs. men 8.4%, $p<0.001$). Of the patients who were diagnosed with a non-ACS diagnoses, 45.4%
7 were classified by a cardiologist, 5.5% by another hospital specialist (e.g. pulmonologist or internal
8 medicine specialist) and the remaining patients were diagnosed by a GP.
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15 *Urgencies*

16 Women and men with chest discomfort were equally sent an ambulance (43.6% vs. 46.6%, $p=0.200$).
17 This was also in women and men who had an ACS (72.9% vs. 70.0%, $p=0.647$), and in those with either
18 ACS or other LTEs (66.4% vs. 67.1%, $p=0.897$). See table 3.
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23 **Discussion**

24 For both sexes, retrosternal pain, pain described as pressing, heavy or tightening, and radiation to the
25 arm were associated with ACS in patients who contacted the OHS-PC for chest discomfort. Radiation to
26 the jaw and severe pain were related to ACS in women. Our results indicate there were more similarities
27 than differences in symptoms associated with the diagnosis ACS for women and men. However, whether
28 these differences have an impact on predicting ACS needs to be further investigated. Women and men
29 with chest discomfort as also those with ACS were equally often sent an ambulance.
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37 Our finding that radiation of pain to the arm and retrosternal ('mid') chest pain were associated with the
38 diagnosis ACS in both sexes was also reported in a study among 2,475 patients with acute chest pain in a
39 multicentre ED-study.²⁵ Another ED-study among 1,334 patients with ACS showed that regardless of
40 ethnics status the most common presenting symptom was retrosternal pain/discomfort of any intensity.
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44 ²⁶ The aforementioned US study in the ED-setting reported that radiation to the arm was associated with
45 ACS in women but not for men, and chest pressure was associated with ACS for men but not in women.
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48 ¹³ The only previously published OHS-PC study reported the opposite; radiation to the arm was
49 associated with ACS in men, but not in women.¹⁷
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51 In our study, women with ACS had more often a history of diabetes and were older than men with ACS,
52 which is in line with other studies.^{8,12} Some studies claim that patients with diabetes more often have
53 atypical symptoms of ACS, however a review of eight studies concluded the evidence of these studies
54 was conflicting.²⁷ We showed that both women and men with diabetes had more often shortness of
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3 breath than those without diabetes, but shortness of breath in patients with diabetes was not
4 associated with ACS. Regarding dispatching the ambulance, the aforementioned OHS-PC study and two
5 EMS studies showed, similar to our findings, that there was no difference in dispatch priorities between
6 men and women with ACS.^{4, 17, 28} This is in contrast with studies that show delay in hospital presentation
7 of women with ACS.^{9, 29}

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13 We need to realize that focusing on gender differences may blur the large overlap in symptoms in
14 women and men. Moreover, comparing *selectively* women with ACS to men with ACS as many previous
15 studies did, is clinically irrelevant.^{9, 14, 30} Clinicians, including GPs, and triage nurses need to know
16 whether and how women with ACS differ from women without ACS, with the same question for men.
17 Nevertheless, even guidelines stick to comparing those with established disease, and express the view
18 that women with ACS more likely present with less specific symptoms than men with ACS.^{1, 31}
19 Unfortunately, public awareness campaigns follow this reasoning, and over-emphasize sex differences in
20 women awareness campaigns ('Go Red for Women' in the United States and 'Invisible me' in Australia).
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Unbalanced attention to symptom differences, neglecting the much larger overlap may even
introduce new blind spots in recognizing ACS in women.³³

A likely reason behind the predominant message that women present with other ACS symptoms than
men is the difference in pathophysiology of coronary artery disease. Women compared to men more
often have elongated plaques, located on bifurcations in epicardial coronaries, coronary spasm,
microvascular dysfunction, and spontaneous coronary dissection.^{32, 34} These pathophysiological
differences have an effect on interventional treatment and prognosis.^{2, 34} However, these differences
do not necessarily imply an effect on symptom presentation because the pain pathway is equal in
women and men: i.e. triggered by myocardial ischemia.^{35, 36} A supply and demand mismatch of the
myocardial oxygen consumption triggers sensory nerve endings in the myocardium and cause ischemia
symptoms, and this is irrespective of the fact whether the ischemia is caused by a plaque rupture in an
epicardial artery or spasm, or any other cause.³⁶ The sex differences in pathophysiology of ACS do
therefore not support the belief in differences in ACS symptoms between women and men.

Another reason behind the belief of 'vague' symptom presentation in women with ACS might be that
they seem to present a larger number of symptoms than men with ACS, and this may be interpreted as
'vague' by physicians.^{15, 37} Presentation of multiple symptoms may influence the prompt recognition of

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3 heart disease and initial actions on the part of health care providers.^{37, 38} In a study from 2018, with
4 2009 women and 976 men hospitalized for myocardial infarction, healthcare providers initially thought
5 symptoms of women (53.4%) were less often heart-related than in men (36.7%).³⁷ In that study women
6 and men had the same chest pain symptoms, but women reported more additional symptoms.³⁷ In our
7 study, the call duration and the number of GP consultations by the triage nurse were similar among
8 women and men, suggesting that triage nurses seem not to experience more difficulties in interpreting
9 symptoms in women than men. This is in line with a prospective study with 2,795 patients with chest
10 discomfort in ED-setting that showed the physicians' diagnostic uncertainty for the presence of ACS in
11 women was not more common as compared to men.³⁹

12 Interestingly, in the majority of calls in our study someone else than the patient called the OHS-PC
13 (women with ACS 69.4%, without ACS 47.7%, and men with ACS 65.8%, and without ACS 52.8%). This
14 was also highlighted in an Australian study among 1,681 patients with an acute myocardial infarction; in
15 90.5% of the women with AMI someone else called on behalf of the patient and in 87.8% of the men
16 with AMI.⁴⁰ According to protocol in OHS-PC, triage nurses ask the patient to the phone, this to prevent
17 loss of (paralinguistic) information from the patient him/herself. In our study, in about 50% of the
18 conversations the patient took over the phone call.

31 *Strengths and limitations*

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33 A major strength is that we could analyse the very initial conversation with symptom presentation of a
34 large sample of patients calling the OHS-PC because of chest discomfort. We analysed the conversations
35 without knowledge of the eventual diagnosis and have prevented risk of hindsight bias of the researcher
36 or recall bias of the patient. Another strength is that we performed gender subgroup analyses combined
37 with interaction analyses across gender, to investigate whether there are indications that ACS related
38 symptoms differ among men and women. Furthermore, our results are generalizable to comparable
39 primary care settings, e.g. UK and Scandinavian countries, and possibly some other European countries.³
40 Our results may even be generalizable to EMS settings, since the prior probability of having an ACS is
41 comparable in EMS setting as in OHS-PC settings.^{4 41}

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51 As the intention of our analysis was to describe whether symptoms were different in patients with ACS
52 from patients without ACS in women and men separately, none of our results can be used to adjust
53 interview questions for the triage nurses. For that purpose, prediction rule development with
54 multivariable analyses is necessary. Also, only with multivariable analysis it can be truly investigated

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3 whether the potential differences are clinically relevant in prediction of ACS. Another limitation is
4 missing values on some clinical variables, a phenomenon common in routine care data, and therefore
5 the results should be interpreted with caution.
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10 **Conclusions**

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12 Our results indicate there were more similarities than differences in symptoms associated with the
13 diagnosis ACS for women and men. Important exceptions were severity and radiation of pain in women.
14 However, whether these differences have an impact on predicting ACS needs to be further investigated
15 with multivariable analyses.
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Data sharing statement

The data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution

FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DC conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript. DC, EdG, AH and RD contributed with and approved the final version of the manuscript. MvS was involved in adjusting the analyses and revising of the manuscript.

References

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S and Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016;37:267-315.
2. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA and Eagle KA. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20-6.
3. Burman RA, Zakariassen E and Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice*. 2014;15:51.
4. Rawshani A, Larsson A, Gelang C, Lindqvist J, Gellerstedt M, Bang A and Herlitz J. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology*. 2014;176:859-65.
5. Mol KA, Smoczynska A, Rahel BM, Meeder JG, Janssen L, Doevendans PA and Cramer MJ. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart*. 2018;5:e000859.
6. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, Sullivan MD, DeLong ER, Bradley EH, Krumholz HM and Peterson ED. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. *Archives of internal medicine*. 2010;170:1834-41.
7. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J and Zaman S. Sex Differences Persist in Time to Presentation, Revascularization, and Mortality in Myocardial Infarction Treated With Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2019;8:e012161.
8. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G and Zheng ZJ. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama*. 2012;307:813-22.
9. Chen W, Woods SL and Puntillo KA. Gender differences in symptoms associated with acute myocardial infarction: a review of the research. *Heart Lung*. 2005;34:240-7.
10. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ and Long T. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Archives of internal medicine*. 2007;167:2405-13.
11. Sorensen NA, Neumann JT, Ojeda F, Schafer S, Magnussen C, Keller T, Lackner KJ, Zeller T, Karakas M, Munzel T, Blankenberg S, Westermann D and Schnabel RB. Relations of Sex to Diagnosis and Outcomes in Acute Coronary Syndrome. *J Am Heart Assoc*. 2018;7.
12. van Oosterhout REM, de Boer AR, Maas A, Rutten FH, Bots ML and Peters SAE. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc*. 2020;9:e014733.
13. Devon HA, Rosenfeld A, Steffen AD and Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *J Am Heart Assoc*. 2014;3:e000586.
14. Araujo C, Laszczynska O, Viana M, Melao F, Henriques A, Borges A, Severo M, Maciel MJ, Moreira I and Azevedo A. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. *BMJ open*. 2018;8:e018798.
15. Canto JG, Canto EA and Goldberg RJ. Time to standardize and broaden the criteria of acute coronary syndrome symptom presentations in women. *Can J Cardiol*. 2014;30:721-8.

16. Ferry AV, Anand A, Strachan FE, Mooney L, Stewart SD, Marshall L, Chapman AR, Lee KK, Jones S, Orme K, Shah ASV and Mills NL. Presenting Symptoms in Men and Women Diagnosed With Myocardial Infarction Using Sex-Specific Criteria. *J Am Heart Assoc.* 2019;8:e012307.
17. van der Meer MG, Appelman Y, Rutten KHG, van der Graaf Y, Nathoe HM, Doevendans PA, Smit M, Verheij E, Botermans A and Rutten FH. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open.* 2019;9:e031613.
18. Erkelens DC, Wouters LT, Zwart DL, Damoiseaux RA, De Groot E, Hoes AW and Rutten FH. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open.* 2019;9:e027477.
19. Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, Malats N, Briggs A, Schroter S, Altman DG, Hemingway H and Group P. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS medicine.* 2013;10:e1001380.
20. Soler JK, Okkes I, Wood M and Lamberts H. The coming of age of ICPC: celebrating the 21st birthday of the International Classification of Primary Care. *Family practice.* 2008;25:312-7.
21. Olagundoye OA, Malan Z, Mash B, van Boven K, Gusso G and Ogunnaike A. Reliability measurement and ICD-10 validation of ICPC-2 for coding/classification of diagnoses/health problems in an African primary care setting. *Family practice.* 2018;35:406-411.
22. van Ierland Y, van Veen M, Huibers L, Giesen P and Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Family practice.* 2011;28:334-41.
23. Keizer E, Maassen I, Smits M, Wensing M and Giesen P. Reducing the use of out-of-hours primary care services: A survey among Dutch general practitioners. *The European journal of general practice.* 2016;22:189-95.
24. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA and Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open Heart.* 2020;7.
25. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Wicki K, Zellweger C, Hoeller R, Moehring B, Sou SM, Mueller M, Denhaerynck K, Meller B, Stallone F, Henseler S, Bassetti S, Geigy N, Osswald S and Mueller C. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. *JAMA Intern Med.* 2014;174:241-9.
26. King-Shier K, Quan H, Kapral MK, Tsuyuki R, An L, Banerjee S, Southern DA and Khan N. Acute coronary syndromes presentations and care outcomes in white, South Asian and Chinese patients: a cohort study. *BMJ open.* 2019;9:e022479.
27. Stephen SA, Darney BG and Rosenfeld AG. Symptoms of acute coronary syndrome in women with diabetes: an integrative review of the literature. *Heart Lung.* 2008;37:179-89.
28. Herlitz J, Starke M, Hansson E, Ringvall E, Karlson BW and Waagstein L. Characteristics and outcome among women and men transported by ambulance due to symptoms arousing suspicion of acute coronary syndrome. *Med Sci Monit.* 2002;8:CR251-6.
29. Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, Zdravkovic M, Milicic D, Dilic M, Manfrini O, Koller A and Badimon L. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc.* 2017;6.
30. Diercks DB, Owen KP, Kontos MC, Blomkalns A, Chen AY, Miller C, Wiviott S and Peterson ED. Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (NCDR ACTION Registry-GWTG). *American heart journal.* 2010;160:80-87 e3.

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2
3 31. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V,
4 Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special
5 Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on
6 Quality of C and Outcomes R. Acute Myocardial Infarction in Women: A Scientific Statement From the
7 American Heart Association. *Circulation*. 2016;133:916-47.
8
9 32. Khamis RY, Ammari T and Mikhail GW. Gender differences in coronary heart disease. *Heart*.
10 2016;102:1142-9.
11 33. Amalberti R. *Navigating safety: necessary compromises and trade-offs – theory and practice*.
12 Heidelberg: Springer; 2013.
13 34. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas
14 AHEM, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V,
15 EUGenMed and Grp CCS. Gender in cardiovascular diseases: impact on clinical manifestations,
16 management, and outcomes. *European heart journal*. 2016;37:24-+.
17 35. Leach A and Fisher M. Myocardial ischaemia and cardiac pain - a mysterious relationship. *Br J*
18 *Pain*. 2013;7:23-30.
19
20 36. Rosen SD. From heart to brain: the genesis and processing of cardiac pain. *Can J Cardiol*.
21 2012;28:S7-19.
22 37. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA
23 and D'Onofrio G. Sex Differences in the Presentation and Perception of Symptoms Among Young
24 Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of
25 Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137:781-790.
26 38. Goldberg R, Goff D, Cooper L, Luepker R, Zapka J, Bittner V, Osganian S, Lessard D, Cornell C,
27 Meshack A, Mann C, Gilliland J and Feldman H. Age and sex differences in presentation of symptoms
28 among patients with acute coronary disease: the REACT Trial. Rapid Early Action for Coronary
29 Treatment. *Coron Artery Dis*. 2000;11:399-407.
30 39. Hillinger P, Twerenbold R, Wildi K, Rubini Gimenez M, Jaeger C, Boeddinghaus J, Nestelberger T,
31 Grimm K, Reichlin T, Stallone F, Puelacher C, Sabti Z, Kozhuharov N, Honegger U, Ballarino P, Miro O,
32 Denhaerynck K, Ekrem T, Kohler C, Bingisser R, Osswald S and Mueller C. Gender-specific uncertainties in
33 the diagnosis of acute coronary syndrome. *Clin Res Cardiol*. 2017;106:28-37.
34 40. Coventry LL, Bremner AP, Jacobs IG and Finn J. Myocardial infarction: sex differences in
35 symptoms reported to emergency dispatch. *Prehosp Emerg Care*. 2013;17:193-202.
36 41. Deakin CD, Sherwood DM, Smith A and Cassidy M. Does telephone triage of emergency (999)
37 calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call
38 prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657
39 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency medicine journal : EMJ*.
40 2006;23:232-5.
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Figure 1. Flowchart study population.

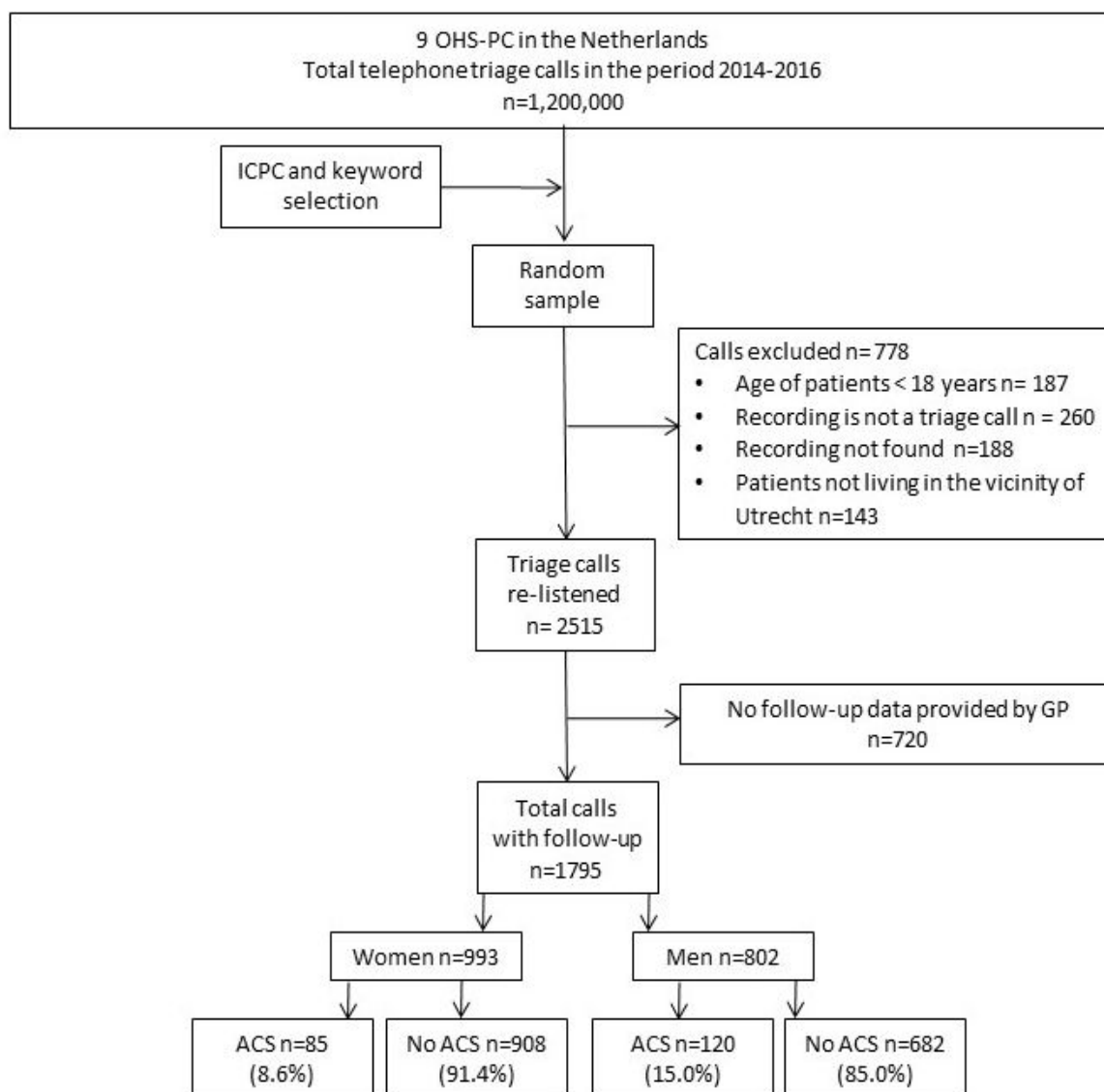


Table 1. Baseline characteristics of 993 (55.3%) women and 802 (44.7%) men patients contacting the OHS-PC with chest discomfort (pain, pressure, tightness, or discomfort)

Characteristics	993 women			Difference (95% CI)	802 men			Difference (95% CI)	P-value interaction gender
	ACS	No ACS	p-value		ACS	No ACS	p-value		
	N = 85 (8.6%)	N = 908 (91.4%)			N = 120 (15.0%)	N = 682 (85.0%)			
Mean age in years (SD)	73.6 (±14.1)	57.8 (±20.1)	<0.001	15.8 (11.4-20.2)	67.2 (±13.0)	56.9 (±19.2)	<0.001	10.3 (6.7-13.9)	0.094
Call characteristics									
Mean call duration in min (SD)	6:47 (±5:16)	7:47 (±3:48)	0.021	1.00 (0.19-1.80)	6:31 (±3:13)	7:33 (±3:42)	0.004	1.02 (0.37-1.68)	0.803
Mean patient's introduction in min (SD)	0:14 (± 0:08)	0:19 (±0:13)	<0.001	0.05 (0.02-0.09)	0:16 (±0:11)	0:19 (±0:14)	0.060	0.03 (0.00-0.06)	0.042
Triage nurse consulted the GP	35 (41.2)	483 (53.2)	0.034	12.0 (0.3-22.9)	64 (53.3)	381 (55.9)	0.607	2.5 (-7.3-12.6)	0.208
Someone else called on behalf of patient	59 (69.4)	433 (47.7)	<0.001	21.7 (10.1-31.6)	79 (65.8)	360 (52.8)	0.008	13.0 (3.0-22.2)	0.251
The patient or person who called expressed concerned (n=922)	36 (97.3)	409 (88.9)	0.109	8.4 (-5.0-12.6)	52 (96.3)	321 (86.5)	0.041	9.8 (-0.9-14.8)	0.935
Chest pain (n=1739)	81 (98.8)	817 (93.1)	0.055	5.7 (-0.8-8.0)	110 (92.4)	624 (94.5)	0.364	2.1 (-2.3-9.0)	0.048
Severe Pain (>7 on a scale 0-10) (n=753)	17 (65.4)	147 (38.1)	0.006	27.3 (5.7-44.7)	13 (23.6)	87 (30.4)	0.312	6.8 (-7.9-18.3)	0.007
Duration									
> 15 min (n=1501)	66 (100)	729 (95.8)	0.102	4.2 (-2.8-6.0)	99 (97.1)	541 (94.6)	0.292	2.5 (-3.8-5.6)	0.998
< 12 hrs (n=1563)	60 (85.7)	575 (72.7)	0.018	13.0 (1.7-20.6)	88 (81.5)	431 (72.6)	0.052	8.9 (-0.6-16.5)	0.490
Location (n=1267)*									

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Retrosternal	33 (62.3)	263 (40.3)	0.002	22.0 (7.1-35.2)	42 (52.5)	191 (39.7)	0.032	12.8 (0.5-24.8)	0.323
Right or left side thorax	14 (26.4)	260 (39.8)	0.054	13.4 (-1.2-24.8)	26 (32.5)	211 (43.9)	0.057	11.4 (-1.0-22.2)	0.757
Type of pain (n=1334)**									
Pressing/heavy/tightening	44 (78.6)	423 (61.5)	0.011	17.1 (3.2-27.2)	78 (82.1)	284 (57.4)	<0.001	24.7 (14.3-32.9)	0.368
Stabbing	8 (14.3)	155 (22.5)	0.152	8.2 (-4.6-16.4)	8 (8.4)	131 (26.5)	<0.001	18.1 (9.2-24.1)	0.141
Radiation of chest pain (n=1391) ***									
Any location	61 (85.9)	485 (68.6)	0.002	17.3 (6.0-25.0)	65 (63.7)	292 (57.1)	0.218	6.6 (-4.5-16.7)	0.071
Arm	31 (75.6)	188 (45.9)	<0.001	29.7 (12.8-42.2)	47 (56.0)	117 (34.8)	<0.001	21.1 (8.7-32.9)	0.339
Between the shoulder blades	11 (52.4)	159 (41.7)	0.336	10.7 (-12.0-32.5)	14 (27.5)	91 (29.4)	0.781	1.9 (-13.4-14.3)	0.352
Jaws	10 (50.0)	66 (22.9)	0.007	27.1 (4.3-49.7)	1 (2.6)	28 (11.3)	0.098	8.7 (-4.6-14.1)	0.015
Shortness of breath (n=1365)	47 (72.3)	455 (66.3)	0.328	6.0 (-7.2-16.7)	53 (60.9)	329 (62.4)	0.788	1.5 (-9.5-13.3)	0.355
Symptoms similar to previous cardiac event (n=748)	13 (32.5)	79 (21.4)	0.108	11.1 (-3.0-28.4)	27 (52.9)	92 (32.1)	0.004	20.8 (5.4-35.8)	0.532
ANS-related symptoms									
Sweating (n=1130)	28 (49.1)	234 (42.5)	0.340	6.6 (-7.4-20.7)	43 (52.4)	170 (38.5)	0.015	13.9 (16.7-25.8)	0.418
Nausea or vomiting (n=808)	16 (44.4)	240 (56.2)	0.173	11.8 (-6.2-28.6)	27 (45.8)	122 (42.7)	0.661	3.1 (-11.1-17.7)	0.186
Pallor or ashen skin (n=652)	20 (55.6)	110 (35.5)	0.019	20.1 (1.9-37.0)	28 (53.8)	103 (40.6)	0.078	13.2 (-2.3-28.3)	0.545
Dizziness or near fainting n=1599)	13 (18.6)	197 (24.4)	0.277	5.8 (-6.0-14.3)	17 (15.9)	127 (20.7)	0.249	4.8 (-4.3-11.9)	0.963
Medical history									

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CV disease or risk factors (n=1461)	54 (78.3)	407 (57.5)	0.001	20.8 (8.4-30.2)	75 (72.1)	359 (61.9)	0.046	10.2 (-0.3-19.3)	0.179
Coronary artery disease (n=966)	17 (42.5)	114 (25.1)	0.017	17.4 (1.7-34.3)	45 (57.0)	151 (38.4)	0.002	18.6 (5.9-30.5)	0.927
Hypertension (n=756)	22 (71.0)	142 (35.1)	<0.001	35.9 (16.0-50.7)	17 (47.2)	94 (33.0)	0.091	14.2 (-3.0-32.1)	0.094
Diabetes mellitus (n=745)	12 (41.4)	56 (14.6)	<0.001	26.8 (9.0-46.5)	12 (28.6)	59 (20.3)	0.220	8.3 (-5.1-25.1)	0.079
Hypercholesterolemia (n=679)	8 (36.4)	81 (23.2)	0.161	13.1 (-5.8-36.4)	19 (45.2)	62 (23.3)	0.003	21.9 (5.8-38.6)	0.527

*P-value comparing retrosternal or left/right side thorax vs. others locations of pain together (retrorsternal, left/right side thorax, back/shoulder, epigastric region)

** Pressing/ heavy/tightening pain vs. other types of pain (stabbing, burning, cramping, tearing). Stabbing pain: stabbing vs. other types of pain (pressing/heavy/tightening, burning, cramping, tearing)

*** P-value comparing radiation arm or back/shoulder or jaws vs. no radiation

NRS: Numeric Rating Scale

ANS-related symptoms: Autonomous nervous system related symptoms

CV disease or risk factors; a history of previous coronary artery disease, heart failure, stroke, cardiac arrhythmia, hypertension, and/or diabetes (patient reported)

Coronary artery disease: History of prior MI, PCI, CABG, stable or unstable angina pectoris (patient reported)

Table 2. Diagnosis of 1,795 patients who contacted the OHS-PC for chest discomfort (pain, pressure, tightness, or discomfort), divided in women and men

	Women n= 993 (55.3%)	Men n=802 (44.7%)	p-value
Acute coronary syndrome	85 (8.6)	120 (15.0)	<0.001
STEMI	16 (18.8)	39 (32.5)	0.037
NSTEMI	41 (48.2)	44 (36.7)	0.114
UAP	17 (20.0)	33 (27.5)	0.250
Non-classified ACS	11 (13.0)	4 (3.3)	0.013
Life threatening events (LTE's)	22 (2.2)	23 (2.9)	0.448
Pulmonary embolism	6 (27.3)	7 (30.4)	0.815
Thoracic aortic dissection	4 (18.2)	2 (8.7)	0.349
Acute abdominal aneurysm	3 (13.6)	2 (8.7)	0.598
Other*	9 (40.9)	12 (52.2)	0.449
Non-urgent cardiovascular diseases**	194 (19.5)	170 (21.2)	0.384
Non-cardiac chest pain, not further specified ***	163 (16.4)	159 (19.8)	0.061
Musculoskeletal pain	199 (20.0)	113 (14.1)	0.001
Psychogenic disorders	139 (14.0)	67 (8.4)	<0.001
Gastrointestinal tract disorders	76 (7.7)	62 (7.7)	0.951
Respiratory tract disorders	52 (5.2)	45 (5.6)	0.727
Other non-urgent diagnoses***	63 (6.3)	43 (5.4)	0.380
*Acute heart failure, stroke, severe COPD exacerbation, sepsis, coronary spasm probably caused by hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.			

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3 ** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension
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5 *** Cardiac pathology unlikely after cardiologist's diagnostic work-up, but without differential diagnosis
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7 **** Amongst others: anaemia, malignancy, vasovagal collapse, side effects medication, dermatologic diseases
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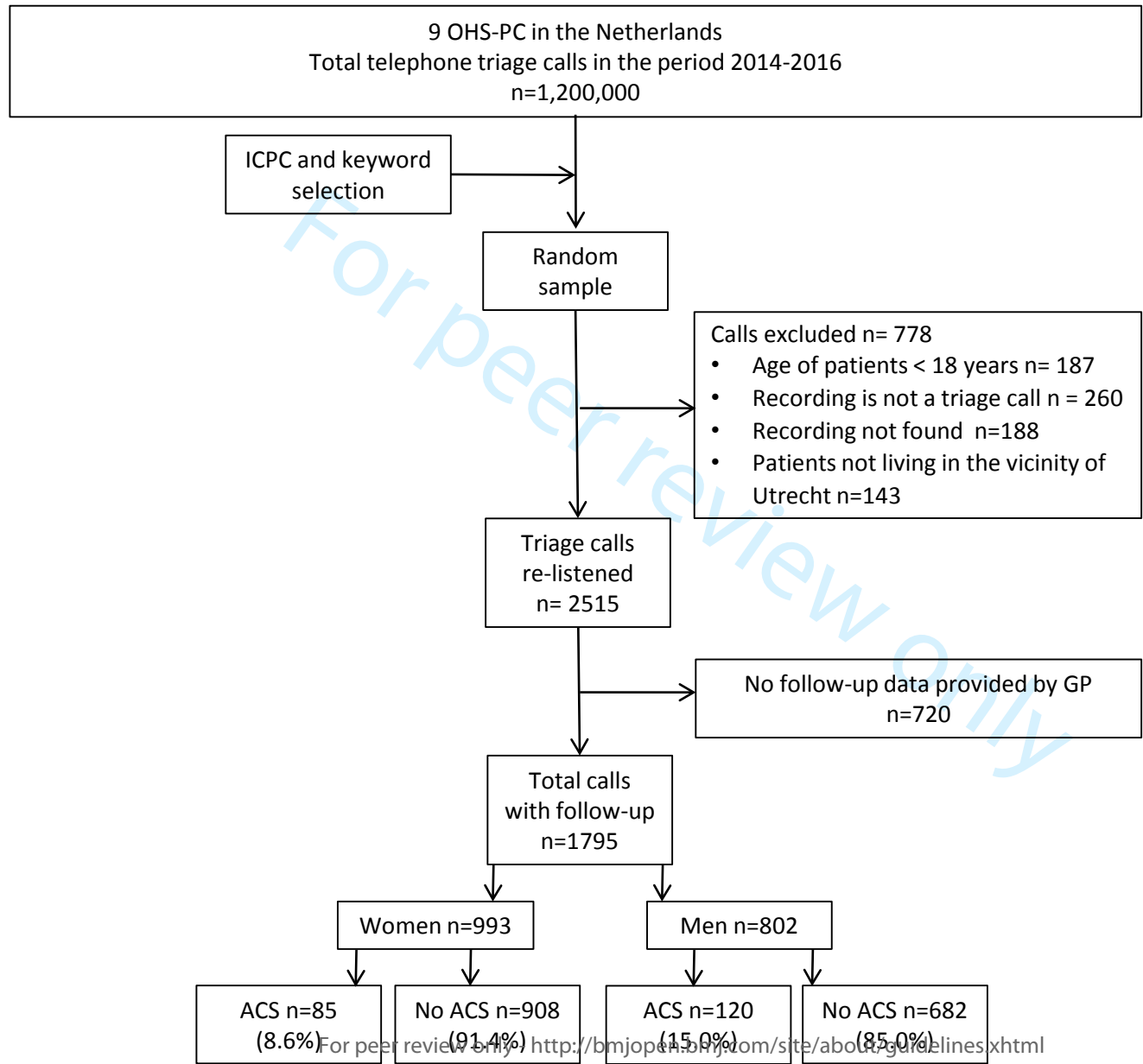
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Table 3. Association between urgency allocation, diagnose ACS and other life threatening events (LTE)

Women	ACS n=85 (8.6%)	No ACS n=908 (91.4%)	p-value 1*	p-value 2**
U1	62 (72.9)	371 (40.9)	<0.001	<0.001
U2	12 (14.1)	231 (25.4)		
U3-U5	11 (13.0)	306 (33.6)		
Men	ACS n=120 (15.0%)	No ACS n=682 (85.0%)		
U1	84 (70.0)	290 (42.5)	<0.001	<0.001
U2	19 (15.8)	142 (20.8)		
U3-U5	17 (14.2)	250 (36.7)		
Women	ACS or LTE n=107 (10.8%)	No ACS or LTE n=886 (89.2%)		
U1	71 (66.4)	362 (40.9)	<0.001	<0.001
U2	21 (19.6)	222 (25.1)		
U3-U5	15 (14.0)	302 (34.0)		
Men	ACS or LTE n=143 (17.8%)	No ACS or LTE n=659 (82.2%)		
U1	96 (67.1)	278 (42.2)	<0.001	<0.001
U2	24 (16.8)	137 (20.8)		
U3-U5	23 (16.1)	244 (37.0)		
* P-value 1: U1 vs. U2, U3, U4 and U5				
** P-value 2: U1,U2 vs. U3,U4,U5				
***LTE = life threatening event. Life threatening events consist of: ACS; pulmonary embolism; thoracic aortic dissection; acute heart failure; stroke; abdominal aortic aneurysm; severe COPD exacerbation; diabetic ketoacidosis; coronary spasm probably caused by hypokalaemia; epileptic insult; bleeding from oesophageal varices; ovarian torsion; ventricular fibrillation.				

Figure 1. Flowchart study population



Supplementary file

Appendix-Table 1: Overview of ICPC-codes used to select calls

ICPC code	Calls of patients with ACS N=205 (%)	Calls of patients without ACS N=1,590 (%)
K01 Pain attributed to the heart	112 (54.6)	485 (30.5)
K02 Pressure/tightness attributed to the heart	39 (19.0)	184 (11.6)
K03 Other cardiovascular pain	1 (0.5)	6 (0.4)
K24 Fear of heart attack	1 (0.5)	8 (0.5)
K74 Angina pectoris	19 (9.3)	101 (6.4)
K75 Acute myocardial infarction	7 (3.4)	22 (1.4)
K76 Other/chronic ischaemic heart disease	0 (0.0)	2 (0.1)
K77 Heart failure	0 (0.0)	11 (0.7)
K93 Pulmonary embolism	0 (0.0)	15 (0.9)
L04 Chest discomfort	25 (12.2)	689 (43.9)
P74 Anxiety disorder	0 (0.0)	12 (0.8)
R02 Shortness of breath	1 (0.5)	36 (2.3)
R98 Hyperventilation	0 (0.0)	10 (0.6)

Appendix-Table 2: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advice given by triage nurse

Appendix-Table 3: Relation of caller to patient in women and men with ACS

	Women n= 85 (8.6%)	Men n = 120 (15.0%)	P-value
Someone else calls on behalf of patient	59 (69.4)	79 (65.8)	0.590
Partner	16 (18.8)	64 (53.3)	<0.001
Son, daughter or other family member	20 (23.5)	8 (6.7)	0.001
Nurse	15 (17.6)	4 (3.3)	<0.001
Other (neighbour, friend, colleague)	8 (9.4)	3 (2.5)	0.030
Patient takes over the phone call on request of the triage nurse	27 (45.8)	58 (73.4)	<0.001

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
/Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	14
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	19 (figure 1)
		(b) Give reasons for non-participation at each stage	19 (figure 1)
		(c) Consider use of a flow diagram	19
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	20,21 (table 1)
Outcome data	15*	Report numbers of outcome events or summary measures	9

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Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study

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3 **Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage:**
4 **a cross-sectional study**
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13 **Competing interest statement**

14 All authors have completed the Unified Competing Interest form and declare no support from any
15 organization for the submitted work; no financial relationships with any organizations that might have
16 an interest in the submitted work in the previous three years, no other relationships or activities that
17 could appear to have influenced the submitted work.
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23 **Transparency declaration**

24 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and
25 transparent account of the study being reported; that no important aspects of the study have been
26 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been
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Abstract

Objectives To identify clinical variables that are associated with the diagnosis acute coronary syndrome (ACS) in women and men with chest discomfort who contact out-of-hours primary care (OHS-PC) by telephone, and to explore whether there are indications whether these variables differ among women and men.

Design Cross-sectional study in which we compared patient and call characteristics of triage call recordings between women with and without ACS, and men with and without ACS.

Setting Nine OHS-PC in the Netherlands.

Participants 993 women and 802 men who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2016.

Primary outcome measure Diagnosis of ACS retrieved from the patient's medical record in general practice, including hospital specialists' discharge letters.

Results Among 1,795 patients (mean age 58.8 (SD 19.5) years, 55.3% women), 15.0% of men and 8.6% of women had an ACS. In both sexes, retrosternal chest pain was associated with ACS (women with ACS vs. without 62.3% vs. 40.3%, $p=0.002$, men with ACS vs. without 52.5% vs. 39.7%, $p=0.032$, gender interaction $p=0.323$), as was pressing/heavy/tightening pain (women 78.6% vs. 61.5%, $p=0.011$, men 82.1% vs. 57.4%, $p<0.001$, gender interaction $p=0.368$) and radiation to the arm (women 75.6% vs. 45.9%, $p<0.001$, men 56.0% vs. 34.8%, $p<0.001$, gender interaction $p=0.339$). Results indicate that only in women, severe pain (65.4% vs. 38.1%, $p=0.006$, gender interaction $p=0.007$) and radiation to jaw (50.0% vs. 22.9%, $p=0.007$, gender interaction $p=0.015$) were associated with ACS. Ambulances were dispatched equally in women (72.9%) and men with ACS (70.0%).

Conclusion Our results indicate there were more similarities than differences in symptoms associated with the diagnosis ACS for women and men. Important exceptions were pain severity and radiation of pain in women. Whether these differences have an impact on predicting ACS needs to be further investigated with multivariable analyses.

Trial number: NTR7331

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3 **Keywords (5): acute coronary syndrome, gender, primary care, telephone triage, chest discomfort**
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7 **Strengths and limitations of this study**
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- 10 • We could analyse the very initial conversation with symptom presentation of a large sample of
11 patients calling for acute chest discomfort, without the risk of hindsight bias of the researcher or
12 recall bias of the patient.
13
 - 14 • We analysed clinical variables associated with ACS in gender subgroup analyses and across
15 gender with statistical interaction terms.
16
 - 17 • Results are generalizable to comparable primary care settings in the United Kingdom and
18 Scandinavian Countries, and our results may even be generalizable to emergency medical
19 service (EMS, '112' or '911') settings.
20
 - 21 • For the purpose of improving telephone triage interviewing, prediction rule development with
22 multivariable regression analysis is needed.
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Introduction

Adequate triage and early diagnosis is key in patients with acute chest discomfort because they might have an acute coronary syndrome (ACS) for which lifesaving early interventions are available. ACS is an umbrella term including ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).¹ For the diagnosis of ACS an abnormal electrocardiogram (ST and/or T wave abnormalities) and/or elevated blood levels of troponin I or T are needed. ACS may then be further subdivided into ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) if the troponin levels are elevated.¹ If troponin levels are not elevated (or increased over time), it is called unstable angina pectoris (UAP).¹ Increased preventive measures and development of (timely) effective therapeutic interventions ('time is muscle') have resulted in improved outcomes and prognosis in ACS.² Telephone triage of patients with chest discomfort, as done in out-of-hours service primary care (OHS-PC) and emergency medical services (EMS or ambulance dispatch centres) is, however, challenging because it is difficult to differentiate ACS from other causes of chest discomfort based on symptoms only.^{3,4} Importantly, the majority of patients with chest discomfort (80%) in the Netherlands first approach the general practitioner (GP) or OHS-PC, and 20% directly calls the ambulance (112) or are self-referrals to the emergency department (ED).⁵

Previous hospital-based studies reported a delayed recognition of ACS in women compared to men.^{6,7} It was suggested that this delayed recognition was related to a less specific presentation in women.^{8,9} This caused an ongoing debate on whether women with ACS compared to men present with less specific symptoms, and how this affects diagnosis, but also treatment, and prognosis.^{10,11} A recent meta-analysis of 27 studies showed that women with ACS compared to men with ACS had higher odds of presenting with pain between the shoulder blades (OR 2.15, 95% CI 1.95-2.37), nausea or vomiting (OR 1.64, 95% CI 1.48-1.82) and shortness of breath (OR 1.34 (95% CI 1.21-1.48)).¹² Women with ACS had lower odds of sweating (OR 0.84, 95% CI 0.76-0.94) and presenting with chest pain (OR 0.70, 95% CI 0.63-0.78), but in both sexes chest pain remained the most common symptom (pooled prevalence men 79% and women 74%).¹² Importantly, researchers suggested standardization in methods of symptoms assessment is needed, because of the difficulties to formulate any definitive statements about symptom presentation, as studies assessed symptoms in different ways (questionnaires or abstracting from medical records).^{9,13-15} Abstracting symptom presentation from medical records may dilute symptom presentation, as they are translated by the clinician in medical terminology.¹⁶ Moreover, many studies suffer from recall or hindsight bias of both patient and researcher as they know the outcome (ACS).

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5 For the clinician or telephone triage nurse it is crucial to differentiate ACS from other causes of chest
6 discomfort. For that, studies are needed that include female and male patients presenting with chest
7 discomfort, in which women and men who turn out to have ACS are compared to those who do not
8 have ACS. Such studies are scarce. In a study performed among patients with chest discomfort seen at
9 the ED in the USA (77 women and 244 men with ACS, and 195 women and 240 men without ACS were
10 compared.¹³ Women with ACS more often reported arm pain than women without ACS (47% vs. 32%,
11 $p=0.021$), while men with ACS reported pressing feeling (63% vs. 54%, $p=0.035$) and chest pain (72% vs
12 60%, $p=0.005$) more often than men without ACS.¹³ In a recent Dutch OHS-PC study among 23 women
13 and 34 men with ACS, and 253 women and 208 men without ACS, symptoms associated with ACS in
14 women and men seemed quite similar and the authors conclude that discriminating ACS in patients with
15 chest discomfort who contacted primary care OHS is difficult in both women and men.¹⁷

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20 We aimed to identify clinical variables that are associated with the diagnosis ACS in women and men
21 with chest discomfort who contact out-of-hours primary care (OHS-PC) by telephone, and to explore
22 whether there are indications these variables differ among women and men. For analyses we used the
23 very initial symptom presentation as available from the recorded telephone triage conversations.

24 25 26 27 28 29 30 31 32 33 34 **Methods**

35 We performed a cross-sectional diagnostic factor study with a random sample of 1,795 OHS-PC calls for
36 chest discomfort (chest pain, pressure, tightness, or discomfort) between 2014 and 2016.^{18,19} We first
37 selected calls on the basis of International Code for Primary Care (ICPC; a WHO world-wide code system
38 for primary care) codes (K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98, appendix-table
39 1) and keywords thoracic pain, chest pain, myocardial infarction, heart attack and their common
40 abbreviations mentioned by the triage nurse in the electronic medical file (EMF) at the OHS-PC.^{20,21}
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42 General practitioners who work at the OHS-PC assign the ICPC codes to the call. We combined ICPC-
43 codes and keywords to achieve a sample with a broad variety of symptoms to capture the entire domain
44 of patients suspected of ACS. We listed all available calls of these patients and assigned random
45 numbers with the Random Number Generator (RAND) function in Microsoft Excel to retrieve a random
46 sample. Calls were excluded before re-listening when the patients' age was below 18 years or when the
47 patient did not live in the surrounding area of the OHS-PCs (because then we could not retrieve a
48 diagnosis from the general practitioner of these patients). Calls were excluded during re-listening when
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3 it not concerned a triage call (e.g. inter-collegial consultation) or when the recording was of poor quality
4 (Figure 1). Adequate methods for sample calculation of a diagnostic factor study is yet lacking. We
5 therefore included a convenient number of patients, that was, at least 80 patients with ACS in each sex
6 category. This number was chosen primarily based for practical and feasibility reasons.
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11 We re-listened the telephone triage recordings to collect information about patient and conversation
12 characteristics, on symptom presentation, medical history, urgency allocation, and involvement of a
13 supervising general practitioner (GP) in the triage conversation. Gender considered the self-identified
14 gender of the patient. Call duration and age were retrieved from the electronic EMF of the OHS-PC. Nine
15 OHS-PC in the Netherlands participated, serving a total population of 1.5 million people. The diagnosis
16 was made after the phone call, which was in the case of ACS nearly always done by the cardiologist
17 (97.1%) in the hospital based on (i) symptom presentation, (i) levels of (high-sensitivity) troponin and (iii)
18 electrocardiography results. The final diagnoses were provided by the patients' GP, based on the
19 electronic medical file including ED and cardiologist discharge letters, and also the notes from the OHS-
20 PC. We used medical information up to 30-days following the contact with the OHS-PC, to allow us to
21 include diagnoses of ACS that was initially missed because the patient was not referred to the
22 cardiologist the same day of the OHS-PC contact. In none of the patients in the study we had evidence of
23 a missed diagnosis of ACS.
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34 35 Context

36 In the Netherlands, OHS-PC covers primary care during 73% of the week hours, and the initial contact is
37 by telephone. In most OHS-PC and EMS, the 'Netherlands Triage Standard' (NTS) is used as a decision
38 support to classify the urgency of the patients' conditions.²² Based on the patient's symptom
39 presentation, the triage nurse needs to choose the most appropriate complaint out of 56 'main
40 complaints'. Each NTS 'main complaint' incorporates a decision tree with hierarchically ordered
41 questions, which are similar for men and women. Triage nurses fill out the caller's responses in the
42 semi-automatic NTS system, which then generates urgency allocations linked to a timeframe within
43 which the patient should be seen by a physician or ambulance personnel (U0 (reanimation) to U5 (self-
44 care advice) appendix-table 2). The triage nurse can overrule this recommendation and up- or
45 downscale the urgency allocation, often after consulting the supervising GP.²³ A recent validation study
46 showed that the diagnostic accuracy of the NTS for patients with chest discomfort is poor (sensitivity
47 0.73 (95% CI 0.68-0.78) and specificity 0.43 (95% CI 0.40-0.45)), as calculated on the outcome ACS or
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3 other life-threatening events (LTEs).²⁴ All telephone calls to the OHS-PC are routinely recorded and
4 archived for five years for training and quality control purposes.
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8 Data analyses

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10 We compared patient and call characteristics between women with and without ACS, and men with and
11 without ACS. For comparison of dichotomous variables we used the Chi² test or Fisher exact test and for
12 continuous variables the independent sample t-test or Mann-Whitney U test. We performed interaction
13 analysis across gender separately for each clinical variable with logistic regression analyses, to explore
14 whether there are indications that these variables are differently associated with the diagnosis ACS
15 among men and women. We analysed the association between urgency allocation and the final
16 diagnosis ACS (alone or including other LTEs) with the Chi² test. We considered pulmonary embolism,
17 thoracic aortic dissection and acute abdominal aneurysm as LTEs; patients with LTEs as well as those
18 with ACS should receive an U1-level urgency.
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20 Data analysis was performed using SPSS, IBM version 25.
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25 Patient and public involvement

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28 No patients were involved in setting the research question or the outcome measures, or in developing
29 plans for design, however, they were involved in the implementation of the study. In addition, they
30 were asked to advise on interpretation and writing up of results. Results will be shared and discussed
31 with the national patient community of cardiovascular diseases ('Harteraad').
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38 Ethics

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40 The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics
41 Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the
42 Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to
43 subjects and could otherwise not be carried out logistically. Personal and research data were handled
44 and stored according to the European General Data Protection Regulation.
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50 **Results**

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52 Among the 1,795 callers with chest discomfort (mean age 58.8 (SD 19.5) years, 55.3% women), 8.6% of
53 women and 15.0% of men had an ACS. In women with an ACS, 18.8% had a STEMI, 48.2% a NSTEMI,
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20.0% an UAP, and 13.0% non-classified ACS. In men with ACS, 32.5% had a STEMI, 36.7% a NSTEMI, 27.5% an UAP, and 3.3% non-classified ACS.

A total of 22 (2.2%) women and 23 men (2.9%) had another LTE than ACS (e.g. pulmonary embolism, thoracic aortic dissection, acute abdominal aneurysm, acute heart failure).

Patient and call characteristics

Men and women with ACS were older than those without ACS (mean age of women with ACS 73.6 vs. without ACS 57.8 years, $p<0.001$, men 67.2 vs. 56.9 years, $p<0.001$, gender interaction $p=0.094$), and the mean duration of the telephone calls was shorter (women 6:47 vs. 7:47 minutes, $p=0.021$, men 6:31 vs. 7:33 minutes, $p=0.004$, gender interaction $p=0.803$) (table 1). The GP was consulted for supervision by the triage nurse in the majority of cases (52.2% in women and 55.5% in men). However, in women with ACS, the GP was less often consulted than in women without ACS (41.2% vs. 53.2%, $p=0.034$), but in men such a difference was not observed (53.3% vs. 55.9%, $p=0.607$, gender interaction $p=0.208$).

In around half of the calls, someone else called initially on behalf of the patient (49.5% in women vs. 54.7% in men). In cases with ACS, for both sexes more often someone else called than in those without ACS (in women 69.4% vs. 47.7%, $p<0.001$, in men 65.8% vs. 52.8%, $p=0.008$, gender interaction $p=0.251$). In men with ACS, most often their female partner (53.3%) called, while in women with ACS, it was either their male partner (17.6%), their daughter (20.0%) or a nurse (17.6%) (appendix-table 3). Callers expressed concerns in nearly all calls, also in those without an ACS; women with ACS vs. women without ACS 97.3% vs. 88.9% ($p=0.109$), and men with ACS vs. men without ACS 96.3% vs. 86.5% ($p=0.041$) (gender interaction $p=0.935$).

Both women and men with ACS had more often a history of coronary artery disease (women 42.5% vs. 25.1%, $p=0.017$, and men 57.0% vs. 38.4%, $p=0.002$, gender interaction $p=0.927$), but women with ACS had more often a history of diabetes (41.4% vs. 14.6%, $p<0.001$, gender interaction $p=0.079$).

Symptom presentation

Chest pain was the most common complaint, both in patients with and without an ACS (women with ACS and without 98.8% and 93.1%, $p=0.055$, in men 92.4% and 94.5%, $p=0.364$, gender interaction $p=0.048$). Retrosternal located chest pain was more common in women and men with ACS than in those without ACS (women 62.3% vs. 40.3%, $p=0.002$, and men 52.5% vs. 39.7%, $p=0.032$, gender interaction $p=0.323$). Also, radiation of pain to the arms was associated with ACS in both sexes (women with vs.

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3 without ACS 75.6% vs. 45.9%, $p < 0.001$, and men 56.0% vs. 34.8%, $p < 0.001$, gender interaction $p = 0.339$,
4 as was pressing/heavy/tightening chest pain (women with vs. without ACS 78.6% vs. 61.5%, $p = 0.011$ and
5 men 82.1% vs. 57.4%, $p < 0.001$, gender interaction $p = 0.368$). Only in women radiation to the jaw had an
6 association with ACS (women 50.0% vs. 22.9%, $p = 0.007$, men 23.6% vs. 30.4%, $p = 0.312$, gender
7 interaction $p = 0.015$) and severe pain (8 or more on a Numeric Rating Scale 0-10) (65.4% vs. 38.1%,
8 $p = 0.006$, men 2.6% vs. 11.3%, $p = 0.098$, gender interaction $p = 0.007$), which had a differential effect
9 towards the risk of ACS in women. Only in men, stabbing pain was very rare in those with ACS (8.4% vs.
10 26.5%, $p < 0.001$,) however this had not have a differential effect on the diagnosis of ACS between men
11 and women (gender interaction $p = 0.141$).

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13 Of the autonomous nervous system (ANS)-related symptoms, nausea/vomiting and dizziness/near
14 fainting were not associated with ACS in either sex. A pale or ashen face was associated with ACS in
15 women (55.6% vs. 35.5%, $p = 0.019$, gender interaction $p = 0.545$), and sweating in men (52.4% vs. 38.1%,
16 $p = 0.015$, gender interaction $p = 0.418$), however without a differential effect on the risk of a diagnosis of
17 ACS between women and men. Recognition of symptoms being similar to a previous cardiac event was
18 associated with ACS in men (52.9% vs. 32.1%, $p = 0.004$), but not clearly for ACS in women (32.5% vs.
19 21.4%, $p = 0.108$, gender interaction $p = 0.532$).

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21 Subgroup analyses in 56 women and 58 men with diabetes showed that both women (85.7% vs. 58.3%,
22 $p < 0.001$) and men with diabetes (67.2% vs. 51.5%, $p = 0.033$, gender interaction $p = 0.119$) more often had
23 shortness of breath than those without diabetes, but as often chest discomfort (women 90.9% vs.
24 95.0%, $p = 0.193$, men 89.2% vs 94.1%, $p = 0.162$, gender interaction $p = 0.969$). Shortness of breath in
25 patients with diabetes was not related to ACS diagnosis (women 81.8% vs. 86.7%, $p = 0.680$, men 75.0%
26 vs. 66.0%, $p = 0.615$, gender interaction $p = 0.520$).

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45 Of the 205 patients with an ACS (85 women, 120 men), 55 (26.8%) patients had a STEMI (women 18.8%,
46 men 32.5%), 85 (41.5%) a NSTEMI (women 48.2%, men 36.7%), 50 (24.4%) unstable angina pectoris
47 (UAP) (women 20.0%, men 27.5%) and 15 (7.3%) unspecified ACS (women 13.0%, men 3.3%), the latter
48 also including two sudden cardiac deaths in women and one in men (Table 2). In nearly all cases (97.1%)
49 the ACS diagnosis was made by a cardiologist based on symptom presentation, troponin levels and
50 electrocardiography. Three patients died before arrival of the ambulance (they were classified as acute
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3 cardiac death) and one patient died after resuscitation at the ED. Two patients were classified as ACS by
4 the GP; they were not referred to the hospital because of short life expectancy due to cancer.

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6 There were 45 patients with other LTEs (2.5%) and the majority of patients had non-urgent medical
7 conditions (86.1%). The most common non-urgent diagnoses in both sexes were (i) non-urgent
8 cardiovascular diseases such as stable angina pectoris, stable heart failure and arrhythmias (19.5% of all
9 female callers with chest discomfort vs. 21.2% of male callers, $p=0.384$) and (ii) non-cardiac unspecified
10 chest pain (women 16.4% vs. 19.8% men, $p=0.061$). Women more often than men were diagnosed with
11 musculoskeletal problems (women 20.8% vs. men 14.1%, $p=0.001$) and psychogenic conditions (women
12 14.0% vs. men 8.4%, $p<0.001$). Of the patients who were diagnosed with a non-ACS diagnoses, 45.4%
13 were classified by a cardiologist, 5.5% by another hospital specialist (e.g. pulmonologist or internal
14 medicine specialist) and the remaining patients were diagnosed by a GP.
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23 *Urgencies*

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25 Women and men with chest discomfort were equally sent an ambulance (43.6% vs. 46.6%, $p=0.200$).
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27 This was also in women and men who had an ACS (72.9% vs. 70.0%, $p=0.647$), and in those with either
28 ACS or other LTEs (66.4% vs. 67.1%, $p=0.897$). See table 3.
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31 **Discussion**

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34 For both sexes, retrosternal pain, pain described as pressing, heavy or tightening, and radiation to the
35 arm were associated with ACS in patients who contacted the OHS-PC for chest discomfort. Radiation to
36 the jaw and severe pain were related to ACS in women. Our results indicate there were more similarities
37 than differences in symptoms associated with the diagnosis ACS for women and men. However, whether
38 these differences have an impact on predicting ACS needs to be further investigated. Women and men
39 with chest discomfort as also those with ACS were equally often sent an ambulance.
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46 Our finding that radiation of pain to the arm and retrosternal ('mid') chest pain were associated with the
47 diagnosis ACS in both sexes was also reported in a study among 2,475 patients with acute chest pain in a
48 multicentre ED-study.²⁵ Another ED-study among 1,334 patients with ACS showed that regardless of
49 ethnics status the most common presenting symptom was retrosternal pain/discomfort of any intensity.
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26 The aforementioned US study in the ED-setting reported that radiation to the arm was associated with
ACS in women but not for men, and chest pressure was associated with ACS for men but not in women.

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3 ¹³ The only previously published OHS-PC study reported the opposite; radiation to the arm was
4 associated with ACS in men, but not in women. ¹⁷

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6 In our study, women with ACS had more often a history of diabetes and were older than men with ACS,
7 which is in line with other studies. ^{8, 12} Some studies claim that patients with diabetes more often have
8 atypical symptoms of ACS, however a review of eight studies concluded the evidence of these studies
9 was conflicting. ²⁷ We showed that both women and men with diabetes had more often shortness of
10 breath than those without diabetes, but shortness of breath in patients with diabetes was not
11 associated with ACS. Regarding dispatching the ambulance, the aforementioned OHS-PC study and two
12 EMS studies showed, similar to our findings, that there was no difference in dispatch priorities between
13 men and women with ACS. ^{4, 17, 28} This is in contrast with studies that show delay in hospital presentation
14 of women with ACS. ^{9, 29}

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16 We need to realize that focusing on gender differences may blur the large overlap in symptoms in
17 women and men. Moreover, comparing *selectively* women with ACS to men with ACS as many previous
18 studies did, is clinically irrelevant. ^{9, 14, 30} Clinicians, including GPs, and triage nurses need to know
19 whether and how women with ACS differ from women without ACS, with the same question for men.
20 Nevertheless, even guidelines stick to comparing those with established disease, and express the view
21 that women with ACS more likely present with less specific symptoms than men with ACS. ^{1, 31}
22 Unfortunately, public awareness campaigns follow this reasoning, and over-emphasize sex differences in
23 women awareness campaigns ('Go Red for Women' in the United States and 'Invisible me' in Australia).
24 ^{7, 30, 32} Unbalanced attention to symptom differences, neglecting the much larger overlap may even
25 introduce new blind spots in recognizing ACS in women. ³³

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27 A likely reason behind the predominant message that women present with other ACS symptoms than
28 men is the difference in pathophysiology of coronary artery disease. Women compared to men more
29 often have elongated plaques, located on bifurcations in epicardial coronaries, coronary spasm,
30 microvascular dysfunction, and spontaneous coronary dissection. ^{32, 34} These pathophysiological
31 differences have an effect on interventional treatment and prognosis. ^{2, 34} However, these differences
32 do not necessarily imply an effect on symptom presentation because the pain pathway is equal in
33 women and men: i.e. triggered by myocardial ischemia. ^{35, 36} A supply and demand mismatch of the
34 myocardial oxygen consumption triggers sensory nerve endings in the myocardium and cause ischemia
35 symptoms, and this is irrespective of the fact whether the ischemia is caused by a plaque rupture in an
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3 epicardial artery or spasm, or any other cause.³⁶ The sex differences in pathophysiology of ACS do
4 therefore not support the belief in differences in ACS symptoms between women and men.
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8 Another reason behind the belief of 'vague' symptom presentation in women with ACS might be that
9 they seem to present a larger number of symptoms than men with ACS, and this may be interpreted as
10 'vague' by physicians.^{15,37} Presentation of multiple symptoms may influence the prompt recognition of
11 heart disease and initial actions on the part of health care providers.^{37,38} In a study from 2018, with
12 2009 women and 976 men hospitalized for myocardial infarction, healthcare providers initially thought
13 symptoms of women (53.4%) were less often heart-related than in men (36.7%).³⁷ In that study women
14 and men had the same chest pain symptoms, but women reported more additional symptoms.³⁷ In our
15 study, the call duration and the number of GP consultations by the triage nurse were similar among
16 women and men, suggesting that triage nurses seem not to experience more difficulties in interpreting
17 symptoms in women than men. This is in line with a prospective study with 2,795 patients with chest
18 discomfort in ED-setting that showed the physicians' diagnostic uncertainty for the presence of ACS in
19 women was not more common as compared to men.³⁹
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22 Interestingly, in the majority of calls in our study someone else than the patient called the OHS-PC
23 (women with ACS 69.4%, without ACS 47.7%, and men with ACS 65.8%, and without ACS 52.8%). This
24 was also highlighted in an Australian study among 1,681 patients with an acute myocardial infarction; in
25 90.5% of the women with AMI someone else called on behalf of the patient and in 87.8% of the men
26 with AMI.⁴⁰ According to protocol in OHS-PC, triage nurses ask the patient to the phone, this to prevent
27 loss of (paralinguistic) information from the patient him/herself. In our study, in about 50% of the
28 conversations the patient took over the phone call.
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41 *Strengths and limitations*

42 A major strength is that we could analyse the very initial conversation with symptom presentation of a
43 large sample of patients calling the OHS-PC because of chest discomfort. We analysed the conversations
44 without knowledge of the eventual diagnosis and have prevented risk of hindsight bias of the researcher
45 or recall bias of the patient. Another strength is that we performed gender subgroup analyses combined
46 with interaction analyses across gender, to investigate whether there are indications that ACS related
47 symptoms differ among men and women. Furthermore, our results are generalizable to comparable
48 primary care settings, e.g. UK and Scandinavian countries, and possibly some other European countries.³
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3 Our results may even be generalizable to EMS settings, since the prior probability of having an ACS is
4 comparable in EMS setting as in OHS-PC settings.^{4 41}
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9 As the intention of our analysis was to describe whether symptoms were different in patients with ACS
10 from patients without ACS in women and men separately, none of our results can be used to adjust
11 interview questions for the triage nurses. For that purpose, prediction rule development with
12 interview questions for the triage nurses. For that purpose, prediction rule development with
13 multivariable analyses is necessary. Also, only with multivariable analysis it can be truly investigated
14 whether the potential differences are clinically relevant in prediction of ACS. Another limitation is
15 missing values on some clinical variables, a phenomenon common in routine care data, and therefore
16 the results should be interpreted with caution.
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23 **Conclusions**

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25 Our results indicate there were more similarities than differences in symptoms associated with the
26 diagnosis ACS for women and men. Important exceptions were pain severity and radiation of pain in
27 women. However, whether these differences have an impact on predicting ACS needs to be further
28 investigated with multivariable analyses.
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Data sharing statement

The data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution

FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DC conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript. DC, EdG, AH and RD contributed with and approved the final version of the manuscript. MvS was involved in adjusting the analyses and revising of the manuscript.

References

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S and Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016;37:267-315.
2. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA and Eagle KA. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20-6.
3. Burman RA, Zakariassen E and Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice*. 2014;15:51.
4. Rawshani A, Larsson A, Gelang C, Lindqvist J, Gellerstedt M, Bang A and Herlitz J. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology*. 2014;176:859-65.
5. Mol KA, Smoczynska A, Rahel BM, Meeder JG, Janssen L, Doevendans PA and Cramer MJ. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart*. 2018;5:e000859.
6. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, Sullivan MD, DeLong ER, Bradley EH, Krumholz HM and Peterson ED. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. *Archives of internal medicine*. 2010;170:1834-41.
7. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J and Zaman S. Sex Differences Persist in Time to Presentation, Revascularization, and Mortality in Myocardial Infarction Treated With Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2019;8:e012161.
8. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G and Zheng ZJ. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama*. 2012;307:813-22.
9. Chen W, Woods SL and Puntillo KA. Gender differences in symptoms associated with acute myocardial infarction: a review of the research. *Heart Lung*. 2005;34:240-7.
10. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ and Long T. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Archives of internal medicine*. 2007;167:2405-13.
11. Sorensen NA, Neumann JT, Ojeda F, Schafer S, Magnussen C, Keller T, Lackner KJ, Zeller T, Karakas M, Munzel T, Blankenberg S, Westermann D and Schnabel RB. Relations of Sex to Diagnosis and Outcomes in Acute Coronary Syndrome. *J Am Heart Assoc*. 2018;7.
12. van Oosterhout REM, de Boer AR, Maas A, Rutten FH, Bots ML and Peters SAE. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc*. 2020;9:e014733.
13. Devon HA, Rosenfeld A, Steffen AD and Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *J Am Heart Assoc*. 2014;3:e000586.
14. Araujo C, Laszczynska O, Viana M, Melao F, Henriques A, Borges A, Severo M, Maciel MJ, Moreira I and Azevedo A. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. *BMJ open*. 2018;8:e018798.
15. Canto JG, Canto EA and Goldberg RJ. Time to standardize and broaden the criteria of acute coronary syndrome symptom presentations in women. *Can J Cardiol*. 2014;30:721-8.

- 1
2
3 16. Ferry AV, Anand A, Strachan FE, Mooney L, Stewart SD, Marshall L, Chapman AR, Lee KK, Jones S,
4 Orme K, Shah ASV and Mills NL. Presenting Symptoms in Men and Women Diagnosed With Myocardial
5 Infarction Using Sex-Specific Criteria. *J Am Heart Assoc.* 2019;8:e012307.
- 6 17. van der Meer MG, Appelman Y, Rutten KHG, van der Graaf Y, Nathoe HM, Doevendans PA, Smit
7 M, Verheij E, Botermans A and Rutten FH. Are there gender disparities in symptom presentation or
8 triage of patients with chest discomfort at primary care out-of-hours services? An observational study.
9 *BMJ open.* 2019;9:e031613.
- 10 18. Erkelens DC, Wouters LT, Zwart DL, Damoiseaux RA, De Groot E, Hoes AW and Rutten FH.
11 Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in
12 out-of-hours primary care: observational design of the Safety First study. *BMJ open.* 2019;9:e027477.
- 13 19. Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, Malats N, Briggs A,
14 Schroter S, Altman DG, Hemingway H and Group P. Prognosis Research Strategy (PROGRESS) 2:
15 prognostic factor research. *PLoS medicine.* 2013;10:e1001380.
- 16 20. Soler JK, Okkes I, Wood M and Lamberts H. The coming of age of ICPC: celebrating the 21st
17 birthday of the International Classification of Primary Care. *Family practice.* 2008;25:312-7.
- 18 21. Olagundoye OA, Malan Z, Mash B, van Boven K, Gusso G and Ogunnaike A. Reliability
19 measurement and ICD-10 validation of ICPC-2 for coding/classification of diagnoses/health problems in
20 an African primary care setting. *Family practice.* 2018;35:406-411.
- 21 22. van Ierland Y, van Veen M, Huibers L, Giesen P and Moll HA. Validity of telephone and physical
22 triage in emergency care: the Netherlands Triage System. *Family practice.* 2011;28:334-41.
- 23 23. Keizer E, Maassen I, Smits M, Wensing M and Giesen P. Reducing the use of out-of-hours
24 primary care services: A survey among Dutch general practitioners. *The European journal of general
25 practice.* 2016;22:189-95.
- 26 24. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA and Zwart DL. Accuracy of
27 telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open Heart.*
28 2020;7.
- 29 25. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Wicki K, Zellweger C,
30 Hoeller R, Moehring B, Sou SM, Mueller M, Denhaerynck K, Meller B, Stallone F, Henseler S, Bassetti S,
31 Geigy N, Osswald S and Mueller C. Sex-specific chest pain characteristics in the early diagnosis of acute
32 myocardial infarction. *JAMA Intern Med.* 2014;174:241-9.
- 33 26. King-Shier K, Quan H, Kapral MK, Tsuyuki R, An L, Banerjee S, Southern DA and Khan N. Acute
34 coronary syndromes presentations and care outcomes in white, South Asian and Chinese patients: a
35 cohort study. *BMJ open.* 2019;9:e022479.
- 36 27. Stephen SA, Darney BG and Rosenfeld AG. Symptoms of acute coronary syndrome in women
37 with diabetes: an integrative review of the literature. *Heart Lung.* 2008;37:179-89.
- 38 28. Herlitz J, Starke M, Hansson E, Ringvall E, Karlson BW and Waagstein L. Characteristics and
39 outcome among women and men transported by ambulance due to symptoms arousing suspicion of
40 acute coronary syndrome. *Med Sci Monit.* 2002;8:CR251-6.
- 41 29. Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, Zdravkovic M, Milicic D, Dilic M,
42 Manfrini O, Koller A and Badimon L. Delayed Care and Mortality Among Women and Men With
43 Myocardial Infarction. *J Am Heart Assoc.* 2017;6.
- 44 30. Diercks DB, Owen KP, Kontos MC, Blomkalns A, Chen AY, Miller C, Wiviott S and Peterson ED.
45 Gender differences in time to presentation for myocardial infarction before and after a national
46 women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification
47 of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) and the
48 National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-
49 Get with the Guidelines (NCDR ACTION Registry-GWTG). *American heart journal.* 2010;160:80-87 e3.
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3 31. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V,
4 Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special
5 Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on
6 Quality of C and Outcomes R. Acute Myocardial Infarction in Women: A Scientific Statement From the
7 American Heart Association. *Circulation*. 2016;133:916-47.
8
9 32. Khamis RY, Ammari T and Mikhail GW. Gender differences in coronary heart disease. *Heart*.
10 2016;102:1142-9.
11 33. Amalberti R. *Navigating safety: necessary compromises and trade-offs – theory and practice*.
12 Heidelberg: Springer; 2013.
13 34. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas
14 AHEM, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V,
15 EUGenMed and Grp CCS. Gender in cardiovascular diseases: impact on clinical manifestations,
16 management, and outcomes. *European heart journal*. 2016;37:24-+.
17 35. Leach A and Fisher M. Myocardial ischaemia and cardiac pain - a mysterious relationship. *Br J*
18 *Pain*. 2013;7:23-30.
19
20 36. Rosen SD. From heart to brain: the genesis and processing of cardiac pain. *Can J Cardiol*.
21 2012;28:S7-19.
22 37. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA
23 and D'Onofrio G. Sex Differences in the Presentation and Perception of Symptoms Among Young
24 Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of
25 Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137:781-790.
26 38. Goldberg R, Goff D, Cooper L, Luepker R, Zapka J, Bittner V, Osganian S, Lessard D, Cornell C,
27 Meshack A, Mann C, Gilliland J and Feldman H. Age and sex differences in presentation of symptoms
28 among patients with acute coronary disease: the REACT Trial. Rapid Early Action for Coronary
29 Treatment. *Coron Artery Dis*. 2000;11:399-407.
30 39. Hillinger P, Twerenbold R, Wildi K, Rubini Gimenez M, Jaeger C, Boeddinghaus J, Nestelberger T,
31 Grimm K, Reichlin T, Stallone F, Puelacher C, Sabti Z, Kozhuharov N, Honegger U, Ballarino P, Miro O,
32 Denhaerynck K, Ekrem T, Kohler C, Bingisser R, Osswald S and Mueller C. Gender-specific uncertainties in
33 the diagnosis of acute coronary syndrome. *Clin Res Cardiol*. 2017;106:28-37.
34 40. Coventry LL, Bremner AP, Jacobs IG and Finn J. Myocardial infarction: sex differences in
35 symptoms reported to emergency dispatch. *Prehosp Emerg Care*. 2013;17:193-202.
36 41. Deakin CD, Sherwood DM, Smith A and Cassidy M. Does telephone triage of emergency (999)
37 calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call
38 prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657
39 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency medicine journal : EMJ*.
40 2006;23:232-5.
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Table 1. Baseline characteristics of 993 (55.3%) women and 802 (44.7%) men patients contacting the OHS-PC with chest discomfort (pain, pressure, tightness, or discomfort)

Characteristics	993 women			Difference (95% CI)	802 men			Difference (95% CI)	P-value interaction gender
	ACS	No ACS	p-value		ACS	No ACS	p-value		
	N = 85 (8.6%)	N = 908 (91.4%)			N = 120 (15.0%)	N = 682 (85.0%)			
Mean age in years (SD)	73.6 (±14.1)	57.8 (±20.1)	<0.001	15.8 (11.4-20.2)	67.2 (±13.0)	56.9 (±19.2)	<0.001	10.3 (6.7-13.9)	0.094
Call characteristics									
Mean call duration in min (SD)	6:47 (±5:16)	7:47 (±3:48)	0.021	1.00 (0.19-1.80)	6:31 (±3:13)	7:33 (±3:42)	0.004	1.02 (0.37-1.68)	0.803
Mean patient's introduction in min (SD)	0:14 (± 0:08)	0:19 (±0:13)	<0.001	0.05 (0.02-0.09)	0:16 (±0:11)	0:19 (±0:14)	0.060	0.03 (0.00-0.06)	0.042
Triage nurse consulted the GP	35 (41.2)	483 (53.2)	0.034	12.0 (0.3-22.9)	64 (53.3)	381 (55.9)	0.607	2.5 (-7.3-12.6)	0.208
Someone else called on behalf of patient	59 (69.4)	433 (47.7)	<0.001	21.7 (10.1-31.6)	79 (65.8)	360 (52.8)	0.008	13.0 (3.0-22.2)	0.251
The patient or person who called expressed concerned (n=922)	36 (97.3)	409 (88.9)	0.109	8.4 (-5.0-12.6)	52 (96.3)	321 (86.5)	0.041	9.8 (-0.9-14.8)	0.935
Chest pain (n=1739)	81 (98.8)	817 (93.1)	0.055	5.7 (-0.8-8.0)	110 (92.4)	624 (94.5)	0.364	2.1 (-2.3-9.0)	0.048
Severe Pain (>7 on a scale 0-10) (n=753)	17 (65.4)	147 (38.1)	0.006	27.3 (5.7-44.7)	13 (23.6)	87 (30.4)	0.312	6.8 (-7.9-18.3)	0.007
Duration									
> 15 min (n=1501)	66 (100)	729 (95.8)	0.102	4.2 (-2.8-6.0)	99 (97.1)	541 (94.6)	0.292	2.5 (-3.8-5.6)	0.998
< 12 hrs (n=1563)	60 (85.7)	575 (72.7)	0.018	13.0 (1.7-20.6)	88 (81.5)	431 (72.6)	0.052	8.9 (-0.6-16.5)	0.490
Location (n=1267)*									

1										
2										
3	Retrosternal	33 (62.3)	263 (40.3)	0.002	22.0 (7.1-35.2)	42 (52.5)	191 (39.7)	0.032	12.8 (0.5-24.8)	0.323
4										
5	Right or left side thorax	14 (26.4)	260 (39.8)	0.054	13.4 (-1.2-24.8)	26 (32.5)	211 (43.9)	0.057	11.4 (-1.0-22.2)	0.757
6										
7	Type of pain (n=1334)**									
8										
9	Pressing/heavy/tightening	44 (78.6)	423 (61.5)	0.011	17.1 (3.2-27.2)	78 (82.1)	284 (57.4)	<0.001	24.7 (14.3-32.9)	0.368
10										
11	Stabbing	8 (14.3)	155 (22.5)	0.152	8.2 (-4.6-16.4)	8 (8.4)	131 (26.5)	<0.001	18.1 (9.2-24.1)	0.141
12										
13	Radiation of chest pain (n=1391) ***									
14										
15	Any location	61 (85.9)	485 (68.6)	0.002	17.3 (6.0-25.0)	65 (63.7)	292 (57.1)	0.218	6.6 (-4.5-16.7)	0.071
16										
17	Arm	31 (75.6)	188 (45.9)	<0.001	29.7 (12.8-42.2)	47 (56.0)	117 (34.8)	<0.001	21.1 (8.7-32.9)	0.339
18										
19	Between the shoulder blades	11 (52.4)	159 (41.7)	0.336	10.7 (-12.0-32.5)	14 (27.5)	91 (29.4)	0.781	1.9 (-13.4-14.3)	0.352
20										
21	Jaws	10 (50.0)	66 (22.9)	0.007	27.1 (4.3-49.7)	1 (2.6)	28 (11.3)	0.098	8.7 (-4.6-14.1)	0.015
22										
23	Shortness of breath (n=1365)	47 (72.3)	455 (66.3)	0.328	6.0 (-7.2-16.7)	53 (60.9)	329 (62.4)	0.788	1.5 (-9.5-13.3)	0.355
24										
25	Symptoms similar to previous cardiac event (n=748)	13 (32.5)	79 (21.4)	0.108	11.1 (-3.0-28.4)	27 (52.9)	92 (32.1)	0.004	20.8 (5.4-35.8)	0.532
26										
27	ANS-related symptoms									
28										
29	Sweating (n=1130)	28 (49.1)	234 (42.5)	0.340	6.6 (-7.4-20.7)	43 (52.4)	170 (38.5)	0.015	13.9 (16.7-25.8)	0.418
30										
31	Nausea or vomiting (n=808)	16 (44.4)	240 (56.2)	0.173	11.8 (-6.2-28.6)	27 (45.8)	122 (42.7)	0.661	3.1 (-11.1-17.7)	0.186
32										
33	Pallor or ashen skin (n=652)	20 (55.6)	110 (35.5)	0.019	20.1 (1.9-37.0)	28 (53.8)	103 (40.6)	0.078	13.2 (-2.3-28.3)	0.545
34										
35	Dizziness or near fainting n=1599)	13 (18.6)	197 (24.4)	0.277	5.8 (-6.0-14.3)	17 (15.9)	127 (20.7)	0.249	4.8 (-4.3-11.9)	0.963
36										
37	Medical history									
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CV disease or risk factors (n=1461)	54 (78.3)	407 (57.5)	0.001	20.8 (8.4-30.2)	75 (72.1)	359 (61.9)	0.046	10.2 (-0.3-19.3)	0.179
Coronary artery disease (n=966)	17 (42.5)	114 (25.1)	0.017	17.4 (1.7-34.3)	45 (57.0)	151 (38.4)	0.002	18.6 (5.9-30.5)	0.927
Hypertension (n=756)	22 (71.0)	142 (35.1)	<0.001	35.9 (16.0-50.7)	17 (47.2)	94 (33.0)	0.091	14.2 (-3.0-32.1)	0.094
Diabetes mellitus (n=745)	12 (41.4)	56 (14.6)	<0.001	26.8 (9.0-46.5)	12 (28.6)	59 (20.3)	0.220	8.3 (-5.1-25.1)	0.079
Hypercholesterolemia (n=679)	8 (36.4)	81 (23.2)	0.161	13.1 (-5.8-36.4)	19 (45.2)	62 (23.3)	0.003	21.9 (5.8-38.6)	0.527

*P-value comparing retrosternal or left/right side thorax vs. others locations of pain together (retrosternal, left/right side thorax, back/shoulder, epigastric region)

** Pressing/ heavy/tightening pain vs. other types of pain (stabbing, burning, cramping, tearing). Stabbing pain: stabbing vs. other types of pain (pressing/heavy/tightening, burning, cramping, tearing)

*** P-value comparing radiation arm or back/shoulder or jaws vs. no radiation

NRS: Numeric Rating Scale

ANS-related symptoms: Autonomous nervous system related symptoms

CV disease or risk factors; a history of previous coronary artery disease, heart failure, stroke, cardiac arrhythmia, hypertension, and/or diabetes (patient reported)

Coronary artery disease: History of prior MI, PCI, CABG, stable or unstable angina pectoris (patient reported)

Table 2. Diagnosis of 1,795 patients who contacted the OHS-PC for chest discomfort (pain, pressure, tightness, or discomfort), divided in women and men

	Women n= 993 (55.3%)	Men n=802 (44.7%)	p-value
Acute coronary syndrome	85 (8.6)	120 (15.0)	<0.001
STEMI	16 (18.8)	39 (32.5)	0.037
NSTEMI	41 (48.2)	44 (36.7)	0.114
UAP	17 (20.0)	33 (27.5)	0.250
Non-classified ACS	11 (13.0)	4 (3.3)	0.013
Life threatening events (LTE's)	22 (2.2)	23 (2.9)	0.448
Pulmonary embolism	6 (27.3)	7 (30.4)	0.815
Thoracic aortic dissection	4 (18.2)	2 (8.7)	0.349
Acute abdominal aneurysm	3 (13.6)	2 (8.7)	0.598
Other*	9 (40.9)	12 (52.2)	0.449
Non-urgent cardiovascular diseases**	194 (19.5)	170 (21.2)	0.384
Non-cardiac chest pain, not further specified ***	163 (16.4)	159 (19.8)	0.061
Musculoskeletal pain	199 (20.0)	113 (14.1)	0.001
Psychogenic disorders	139 (14.0)	67 (8.4)	<0.001
Gastrointestinal tract disorders	76 (7.7)	62 (7.7)	0.951
Respiratory tract disorders	52 (5.2)	45 (5.6)	0.727
Other non-urgent diagnoses***	63 (6.3)	43 (5.4)	0.380
*Acute heart failure, stroke, severe COPD exacerbation, sepsis, coronary spasm probably caused by hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.			

1
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3 ** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension
4

5 *** Cardiac pathology unlikely after cardiologist's diagnostic work-up, but without differential diagnosis
6

7 **** Amongst others: anaemia, malignancy, vasovagal collapse, side effects medication, dermatologic diseases
8
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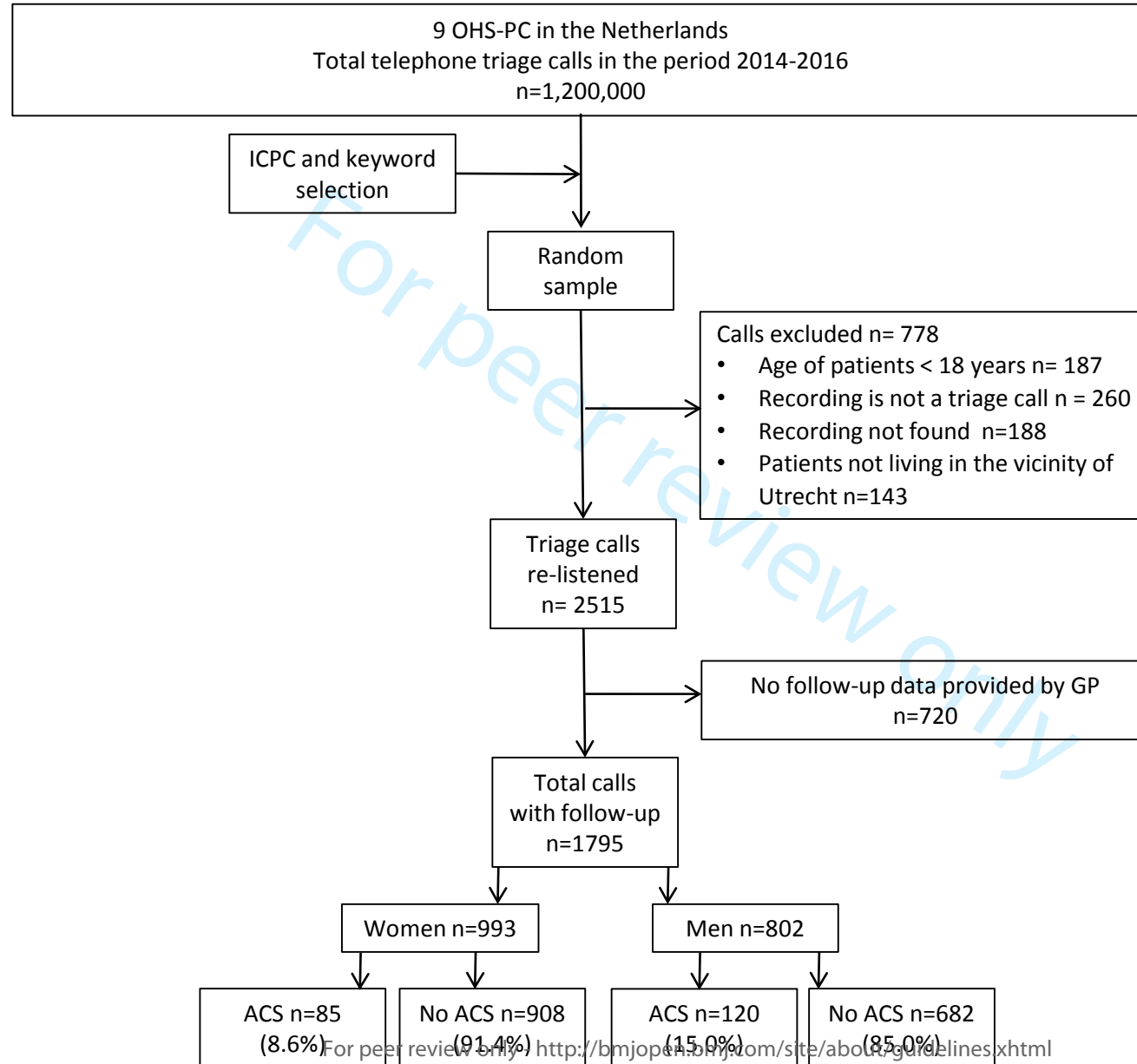
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Table 3. Association between urgency allocation, diagnose ACS and other life threatening events (LTE)

Women	ACS n=85 (8.6%)	No ACS n=908 (91.4%)	p-value 1*	p-value 2**
U1	62 (72.9)	371 (40.9)	<0.001	<0.001
U2	12 (14.1)	231 (25.4)		
U3-U5	11 (13.0)	306 (33.6)		
Men	ACS n=120 (15.0%)	No ACS n=682 (85.0%)		
U1	84 (70.0)	290 (42.5)	<0.001	<0.001
U2	19 (15.8)	142 (20.8)		
U3-U5	17 (14.2)	250 (36.7)		
Women	ACS or LTE n=107 (10.8%)	No ACS or LTE n=886 (89.2%)		
U1	71 (66.4)	362 (40.9)	<0.001	<0.001
U2	21 (19.6)	222 (25.1)		
U3-U5	15 (14.0)	302 (34.0)		
Men	ACS or LTE n=143 (17.8%)	No ACS or LTE n=659 (82.2%)		
U1	96 (67.1)	278 (42.2)	<0.001	<0.001
U2	24 (16.8)	137 (20.8)		
U3-U5	23 (16.1)	244 (37.0)		
* P-value 1: U1 vs. U2, U3, U4 and U5				
** P-value 2: U1,U2 vs. U3,U4,U5				
***LTE = life threatening event. Life threatening events consist of: ACS; pulmonary embolism; thoracic aortic dissection; acute heart failure; stroke; abdominal aortic aneurysm; severe COPD exacerbation; diabetic ketoacidosis; coronary spasm probably caused by hypokalaemia; epileptic insult; bleeding from oesophageal varices; ovarian torsion; ventricular fibrillation.				

Figure 1. Flowchart study population



Supplementary file

Appendix-Table 1: Overview of ICPC-codes used to select calls

ICPC code	Calls of patients with ACS N=205 (%)	Calls of patients without ACS N=1,590 (%)
K01 Pain attributed to the heart	112 (54.6)	485 (30.5)
K02 Pressure/tightness attributed to the heart	39 (19.0)	184 (11.6)
K03 Other cardiovascular pain	1 (0.5)	6 (0.4)
K24 Fear of heart attack	1 (0.5)	8 (0.5)
K74 Angina pectoris	19 (9.3)	101 (6.4)
K75 Acute myocardial infarction	7 (3.4)	22 (1.4)
K76 Other/chronic ischaemic heart disease	0 (0.0)	2 (0.1)
K77 Heart failure	0 (0.0)	11 (0.7)
K93 Pulmonary embolism	0 (0.0)	15 (0.9)
L04 Chest discomfort	25 (12.2)	689 (43.9)
P74 Anxiety disorder	0 (0.0)	12 (0.8)
R02 Shortness of breath	1 (0.5)	36 (2.3)
R98 Hyperventilation	0 (0.0)	10 (0.6)

Appendix-Table 2: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advice given by triage nurse

Appendix-Table 3: Relation of caller to patient in women and men with ACS

	Women n= 85 (8.6%)	Men n = 120 (15.0%)	P-value
Someone else calls on behalf of patient	59 (69.4)	79 (65.8)	0.590
Partner	16 (18.8)	64 (53.3)	<0.001
Son, daughter or other family member	20 (23.5)	8 (6.7)	0.001
Nurse	15 (17.6)	4 (3.3)	<0.001
Other (neighbour, friend, colleague)	8 (9.4)	3 (2.5)	0.030
Patient takes over the phone call on request of the triage nurse	27 (45.8)	58 (73.4)	<0.001

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
/Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	14
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	19 (figure 1)
		(b) Give reasons for non-participation at each stage	19 (figure 1)
		(c) Consider use of a flow diagram	19
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	20,21 (table 1)
Outcome data	15*	Report numbers of outcome events or summary measures	9

1			
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
3			n.a.
4			
5			
6			
7			
8			(b) Report category boundaries when continuous variables were categorized
9			20,21 (table 1)
10			
11			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
12			NA
13	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
14			9,10 (subgroup diabetes)
15	Discussion		
16	Key results	18	Summarise key results with reference to study objectives
17			11
18	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
19			14
20			
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22			13,14
23			
24			
25	Generalisability	21	Discuss the generalisability (external validity) of the study results
26			14
27	Other information		
28	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
29			2
30			
31			

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.