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Gender-stratified analyses of symptoms associated with life-threatening events in patients calling out-of-hours primary care for shortness of breath

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Abstract

Background Women and men seem to perceive shortness of breath (SOB) differently. However, it is unknown whether symptom presentation varies between genders during a life-threatening event (LTE).

Aim To assess whether symptoms associated with an LTE vary between women and men with SOB calling out-of-hours primary care (OHS-PC).

Methods Cross-sectional study including data from patients contacting two large Dutch OHS-PC centres for SOB between 1 September 2020 and 31 August 2021. We compared symptoms mentioned during triage conversations between patients with and without LTEs (amongst others, acute coronary syndrome, pulmonary embolism, acute heart failure and severe pneumonia), stratified by gender.

Results We included 1,861 adults contacting OHS-PC for SOB (mean age 53.3 years, 55.3% women). The risk of an LTE was lower in women than in men (15.0% vs. 18.7%, RR 0.80; 95% CI 0.65–0.98). Patients with LTEs were older, more often had someone else calling for them, a history of cardiovascular disease, cardiovascular medication use and inability to speak full sentences compared to those without LTEs. Differences between women and men were only apparent for calling at night (women: 24.0% vs. 15.2%, p = 0.006, versus men: 18.7% vs. 22.5%, p = 0.300; p-value interaction term: 0.009) and participation of general practitioners during telephone triage (women: 49.4% vs. 49.5%, p = 0.975, versus men: 56.1% vs. 43.0%, p = 0.003; p-value interaction term: 0.033).

Conclusions Among patients contacting OHS-PC with SOB, about 1 in 6 had an LTE, more often men than women. We found no strong evidence of symptom differences between gender groups predictive of LTEs.

Trial registration The Netherlands Trial Register, number: NL9682, registration date: 20–08-2021.

Keywords Gender-differences, General practice, Out-of-hours primary care, Shortness of breath, Telephone triage

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Background

Shortness of breath (SOB) is a common reason for patients to call out-of-hours primary care (OHS-PC). In the Netherlands, it is the prime reason for home visits by general practitioners (GPs). [1, 2] Furthermore, SOB is the second most common reason for sending an ambulance after a call to the OHS-PC, accounting for 8% of all ambulances sent in the Netherlands. [1] A recent cross-sectional study conducted in Denmark further highlighted the significant workload associated with SOB in primary care, showing that 79% of patient contacts related to SOB required a face-to-face consultation with a GP. [3] This huge workload, together with the apparent risk of urgent conditions requiring the dispatch of ambulances in some patients, requires effective triage. As an exemplification of this, important critical medical conditions may underlie SOB such as acute coronary syndrome (ACS), acute heart failure, pulmonary embolism and severe exacerbation of asthma or COPD. [4–6] Triage in this setting, however, is currently suboptimal as previous studies showed that in callers with SOB 46% of the patients with a life-threatening event (LTE) did not receive a high urgency (undertriage), while on the other hand, 35% of patients without an LTE received a high urgency (overtriage). [7] An explanation for this suboptimal telephone triage could lie in the limited diagnostic value of symptoms alone in conditions such as pulmonary embolism. Previous research has shown that even well-known clinical decision rules, such as the Wells or Geneva scores, include variables with only modest likelihood ratios (typically around 2), indicating limited individual discriminative power. [8, 9].

One of the plausible reasons why this triaging in SOB is so difficult likely originates in the fact that it is such a subjective symptom. Indeed, respiratory distress is experienced and expressed variably by patients. [10, 11] Perceived severity may also differ between women and men. Prior studies indicated that women perceive asthma symptoms as more bothersome than men while the objective measures of asthma severity and lung function, such as forced expiratory volume in one second (FEV1) were comparable. [12, 13] Similarly, standardized task-based questionnaires reported a higher symptom severity perception among women compared to men with COPD. [14–16] Another gender-related difference in the perception of symptoms was that women with an ACS were less likely to consider their symptoms to be related to a heart-related problem than men. [17].

There are also important biological differences between women and men, such as anatomy and hormonal variations that can cause differences in health and disease manifestations. [18] Women of similar stature as men possess smaller lungs, narrower airways, weaker respiratory muscles, and a reduced surface area for pulmonary gas exchange, all of which may affect SOB or related symptoms. [19–23].

However, it is unclear whether these differences between gender in biological factors and perception of SOB also lead to a difference in symptomatology between women and men experiencing an LTE. Numerous studies have assessed differences in symptom presentation of women and men with an established respiratory or cardiovascular LTE. [10, 24–29] However, these gender-related comparisons are clinically irrelevant for triage; then one needs to know how among women or men with SOB, those with an LTE differ from those without an LTE. Such studies are currently lacking.

We therefore assessed in both women and men whether patient and call characteristics, medical history, medication use, and symptoms differed between those with and without an LTE when calling OHS-PC for SOB.

Methods

Study design

This study is part of the Opticall study, a multiple methods study aimed at describing and improving telephone triage of callers with SOB in Dutch OHS-PC. The rationale and design of this study are published elsewhere. [30] The objective of the current cross-sectional study was to assess whether patient and call characteristics, medical history, medication use, and symptoms, predictive for LTE, varied across women and men who contacted the OHS-PC for SOB.

Setting

Outside regular working hours, OHS-PC centres provide urgent primary care to ensure 24/7 medical access. In the Netherlands, as in many other European countries, OHS-PC is organised in large-scale cooperatives. [31] Under the supervision of a GP, triage nurses assess the urgency of the patient's health problem by telephone and decide whether the patient should be seen by a GP or by another medical professional, within what time frame, and what type of contact is needed (immediate ambulance, home visit, consultation with a GP or telephone advice). [32].

Study population

In this cross-sectional study, we included data of adults who called two Dutch OHS-PC centres with SOB between 1 September 2020 and 31 August 2021 if their telephone conversation was for triage (e.g., not a consultation with ambulance personnel) and in whom follow-up data about the final diagnosis could be retrieved from the patients' own GP's electronic health record (EHR). [33, 34] We excluded patients whose triage conversation was either not traceable in the computer system or performed in a language other than Dutch or English.

Data collection

Data was collected from both the OHS-PC and general practices. Patient and call characteristics, medical history, medication use, and symptoms were collected from re-listened call recordings and OHS-PC EHR. These data were extracted by trained medical students or medical doctors. To enhance validity, a random sample of 10% the call recordings was independently reviewed by a second researcher. Any disagreements were resolved by discussion with a third researcher.

If a variable was not mentioned during the telephone triage conversation, it was labelled as missing and the case was excluded from the analysis of that specific variable. Data from call recordings were linked to follow-up data about final diagnosis and hospitalization within 30 days of the index contact with the OHS-PC from the patients' own primary care EHR.

Outcome measures

Primary outcome was the association between patient and call characteristics, medical history, medication use, and symptoms and the presence of LTEs (yes versus no) among women and men who called OHS-PC with SOB.

We considered the following diagnoses as an LTE: pulmonary embolism, ACS, acute heart failure, transient ischemic attack, stroke, sepsis, anaphylaxis, pneumothorax, subcutaneous emphysema, gastrointestinal bleeding, Takotsubo cardiomyopathy, perforated diverticulitis, respiratory insufficiency due to reduced consciousness, and severe anaemia. The diagnoses COVID-19, pneumonia and asthma/COPD exacerbation were classified as either mild to moderate or severe. Severe cases were defined as those requiring hospitalisation or administration of supplementary oxygen at home within 24 h and were classified as LTE. The diagnosis heart failure was classified as either stable or acute, and acute cases were classified as LTE.

Data analysis

First, we used Pearson's chi-square tests and independent sample T-tests to evaluate the differences in gender and age of eligible triage conversations included in the analysis against eligible conversations not included in the analysis.

The number of OHS-PC contacts between the genders were compared with the Binomial test. For the comparison of the prevalence of specific diagnoses, the Pearson's chi-square test was used, and in case of small groups with less than 10 people, the Fisher's exact test. We calculated relative risks (RRs) with accompanying 95% confidence intervals (CI) to analyse the relation between gender and the presence of LTEs.

Patient and call characteristics, medical history, medication use, and symptoms were described descriptively. Variables discussed in less than 5% of the triage calls were excluded from analyses. All remaining variables were compared between patients with and without LTE, stratified according to gender. Pearson's chi-square tests or Fisher's exact tests (in case of groups with less than 10 people) were used to compare categorical variables. Independent sample T-tests were used to compare continuous variables. Logistic regression models with interaction terms between gender and all variables separately were used to assess whether the association between these variables and the outcome LTE was statistically different in women compared to men.

Since the relation between age and the presence of LTEs is unlikely to be linear, we analysed this relation at a more detailed level. For this, we built a prediction model with gender, age as a cubic spline function with four knots on the 0.05, 0.35, 0.65 and 0.95 percentiles and an interaction term between age and gender. A restricted cubic spline function allows for flexible curve fitting without assuming a strictly linear association, thereby providing a more accurate representation of complex relations in the data.

A p-value of < 0.05 was considered statistically significant. All data analyses were performed with SPSS statistics version 29.0.1 and R version 4.3.2 ('rms' and 'ggplot2' packages).

Patient and public involvement

Patients were involved as advisors during this study. [35] We organized advisory board meetings for relevant stakeholders including patient representatives. During these meetings, the stakeholders were invited to provide input on the conduct of this study and the communication plans.

Ethics

The Medical Ethics Committee (MREC) Utrecht (reference number 21/361) has reviewed our study protocol. The MREC concluded that this study is not within the scope of the WMO and granted an exemption for this study. We used a waiver for informed consent (this exception to the informed consent has been described in The Declaration of Helsinki and is further specified in the CIOMS guideline which contains a part about waiving informed consent). [36, 37] Personal data and research data was de-identified according to the European General Data Protection Regulation.

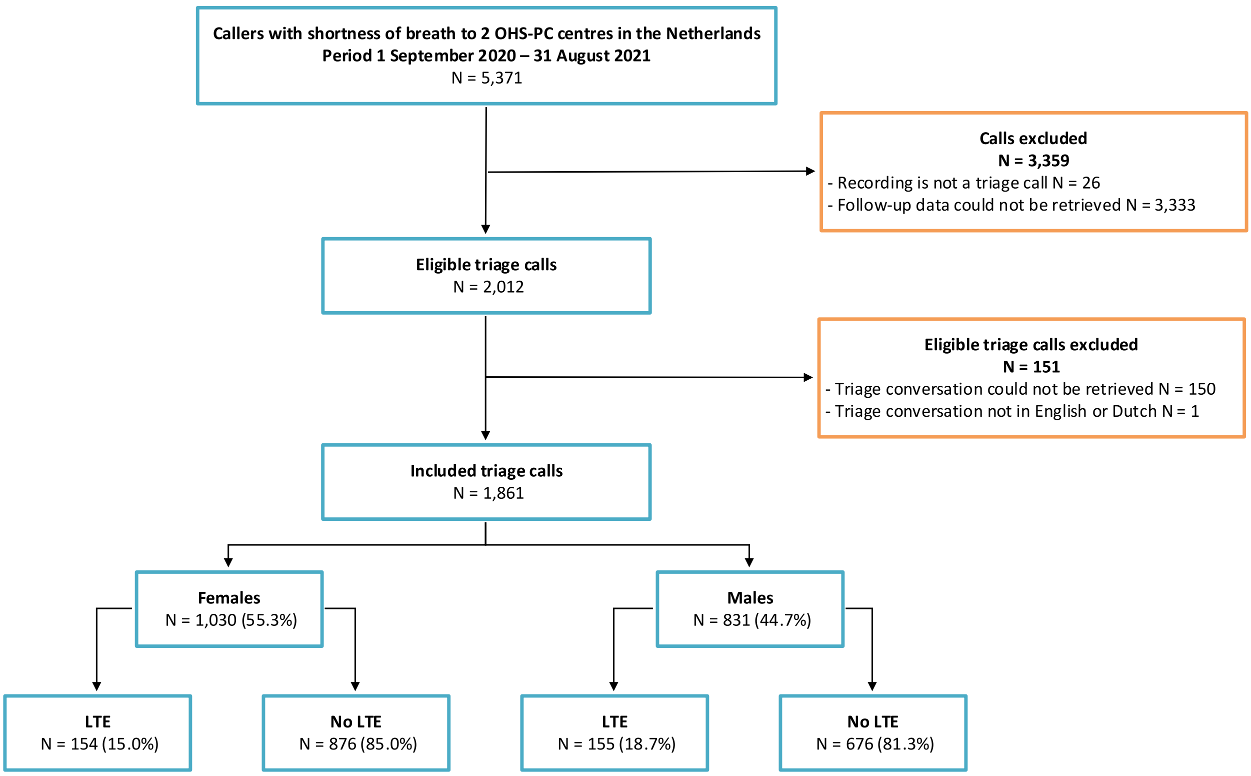

Fig. 1 Flowchart of study population

Results

A total of 2,012 patient calling OHS-PC were eligible, of which 1,861 patients were included in the analyses (Fig. 1).

The patient characteristics age and gender of patients included in the study did not significantly differ from patients who were eligible but could not be included (age: 53.3 (standard deviation (SD) 21.5) vs 56.3 (SD 22.5) years, $p = 0.069$; women: 55.3% vs. 60.2%, $p = 0.242$).

Based on the 1,861 included triage conversations, women with SOB more often called OHS-PC than men with SOB (1,030 (55.3%) vs. 831 (44.7%), $p < 0.001$), and the mean age was 53.3 (SD 21.5) years; 52.5 (SD 22.0) years in women and 54.4 (SD 20.9) years in men.

Life-threatening events and diagnoses

Of all patients calling with SOB, women less often had an LTE than men (15.0% vs. 18.7%, relative risk (RR) 0.80; 95% CI 0.65–0.98). The most common LTEs among both women and men were severe COVID-19 infection (6.0%), acute heart failure (2.6%), severe COPD exacerbation (2.0%) and severe pneumonia (1.8%), while the most common non-LTEs are mild or moderate COVID-19 infection (21.1%) and unspecified shortness of breath (11.5%).

Women compared to men more often had an upper respiratory tract infection (6.7% vs. 4.2%, $p = 0.020$), unspecified chest pain (5.4% vs. 3.5%, $p = 0.045$) and unspecified shortness of breath (12.8% vs. 9.9%, $p = 0.048$). Contrary, men compared to women more often had a severe COVID-19 infection (7.6% vs. 4.7%, $p = 0.008$), an ACS (1.2% vs. 0.3%, $p = 0.024$) and SOB due to (existing) cancer (2.5% vs. 1.3%, $p = 0.043$). See Table 1 and Fig. 2.

Patient and call characteristics

An overview of patient and call characteristics, medical history, medication use and symptoms of patients calling OHS-PC with SOB, stratified by gender, is presented in Table 2.

Patients with LTEs were on average older than those without LTEs (women: 66.7 ((SD) 18.7) vs. 50.0 (SD 21.6) years, $p < 0.001$; men: 62.8 (SD 17.7) vs. 52.5 (SD 21.1) years, $p < 0.001$; p-value interaction term: 0.061). Irrespective of gender, the risk of LTEs increased with age. In men, the prevalence increased from 20 years onwards and stabilised around 75 years with a peak prevalence of LTE of 27% at the age of 76.8 years. In women, the prevalence increased from 40 years onwards and peaked at 76.0 years at a prevalence of LTE 30%, after which the

Table 1 Final diagnoses of women and men calling OHS-PC with shortness of breath

	Total $n = 1{,}861$	**Women** $n = 1{,}030$ **(55.3%)**	**Men** $n = 831$ **(44.7%)**	***p*-value**
Life-threatening events	309 (16.6%)	154 (15.0%)	155 (18.7%)	0.033‡
Cardiovascular disorders				
Acute coronary syndrome	13 (0.7%)	3 (0.3%)	10 (1.2%)	0.024†
Acute heart failure	48 (2.6%)	27 (2.6%)	21 (2.5%)	0.898‡
Respiratory tract disorders				
Severe asthma exacerbation	11 (0.6%)	9 (0.9%)	2 (0.2%)	0.125†
Severe COPD exacerbation	38 (2.0%)	19 (1.8%)	19 (2.3%)	0.503‡
Severe COVID-19 infection	111 (6.0%)	48 (4.7%)	63 (7.6%)	0.008‡
Severe pneumonia	34 (1.8%)	20 (1.9%)	14 (1.7%)	0.681‡
Other disorders				
Anaphylaxis	14 (0.8%)	8 (0.8%)	6 (0.7%)	1.000†
Pulmonary embolism	17 (0.9%)	7 (0.7%)	10 (1.2%)	0.327†
Sepsis	11 (0.6%)	6 (0.6%)	5 (0.6%)	1.000†
Other life-threatening events (LTEs)*	12 (0.6%)	7 (0.7%)	5 (0.6%)	1.000†
Non-urgent disorders	1,552 (83.4%)	876 (85.0%)	676 (81.3%)	0.033‡
Cardiovascular disorders				
Stable heart failure	40 (2.1%)	23 (2.2%)	17 (2.0%)	0.782‡
Respiratory tract disorders				
Mild or moderate asthma exacerbation	119 (6.4%)	59 (5.7%)	60 (7.2%)	0.191‡
Mild or moderate COPD exacerbation	95 (5.1%)	54 (5.2%)	41 (4.9%)	0.763‡
Mild or moderate COVID-19 infection**	393 (21.1%)	212 (20.6%)	181 (21.8%)	0.529‡
Mild or moderate pneumonia	81 (4.4%)	41 (4.0%)	40 (4.8%)	0.381‡
Upper respiratory tract infection	104 (5.6%)	69 (6.7%)	35 (4.2%)	0.020‡
Other disorders				
Hyperventilation/anxiety/stress	137 (7.4%)	75 (7.3%)	62 (7.5%)	0.883‡
Shortness of breath due to (existing) cancer	34 (1.8%)	13 (1.3%)	21 (2.5%)	0.043‡
Unspecified chest pain***	85 (4.6%)	56 (5.4%)	29 (3.5%)	0.045‡
Unspecified shortness of breath****	214 (11.5%)	132 (12.8%)	82 (9.9%)	0.048‡
Other non-urgent disorders*****	250 (13.4%)	142 (13.8%)	108 (13.0%)	0.619‡

LTE Life-threatening event, *OHS-PC* Out-of-hours primary care

* Transient ischaemic attack, stroke, pneumothorax, subcutaneous emphysema, gastro-intestinal bleeding, Takotsubo cardiomyopathy, perforated diverticulitis, respiratory insufficiency due to reduced consciousness, severe anaemia

** Proven (most cases) and suspected COVID-19 infections

*** Cardiac pathology unlikely after cardiologist's or GP's diagnostic work-up, including those with musculoskeletal chest pain

**** Cardiac or pulmonary pathology unlikely after cardiologist's, pulmonologists, or GP's diagnostic work-up

***** Amongst others: atrial fibrillation or atrial flutter, gastro-oesophageal reflux, costal contusion/fracture, bronchitis or bronchial hyperreactivity, shortness of breath due to terminal phase, hay fever

† Fisher's exact test

‡Pearson's chi-square test

risk somewhat decreased again to a prevalence of around 27% (Fig. 3).

Patients with LTE more often had someone else calling for them (women: 70.6% vs. 43.1%, $p < 0.001$; men: 78.1% vs. 50.5%, $p < 0.001$; p-value interaction term: 0.732).

Women less often had an LTE than men (15.0% vs. 18.7%, relative risk (RR) 0.80; 95% CI 0.65–0.98). Women calling at night more often had an LTE (24.0% vs. 15.2%, $p = 0.006$), which was not seen in men (18.7% vs. 22.5%, $p = 0.300$; p-value interaction term: 0.009). The GP more often participated in telephone triage of men with an LTE (56.1% vs. 43.0%, $p = 0.003$), but not of women with an LTE (49.4% vs. 49.5%, p = 0.975; p-value interaction term: 0.033).

Medical history and medication use

Patients with LTEs more often had a history of cardiovascular disease (women: 55.9% vs. 29.0%, $p < 0.001$;

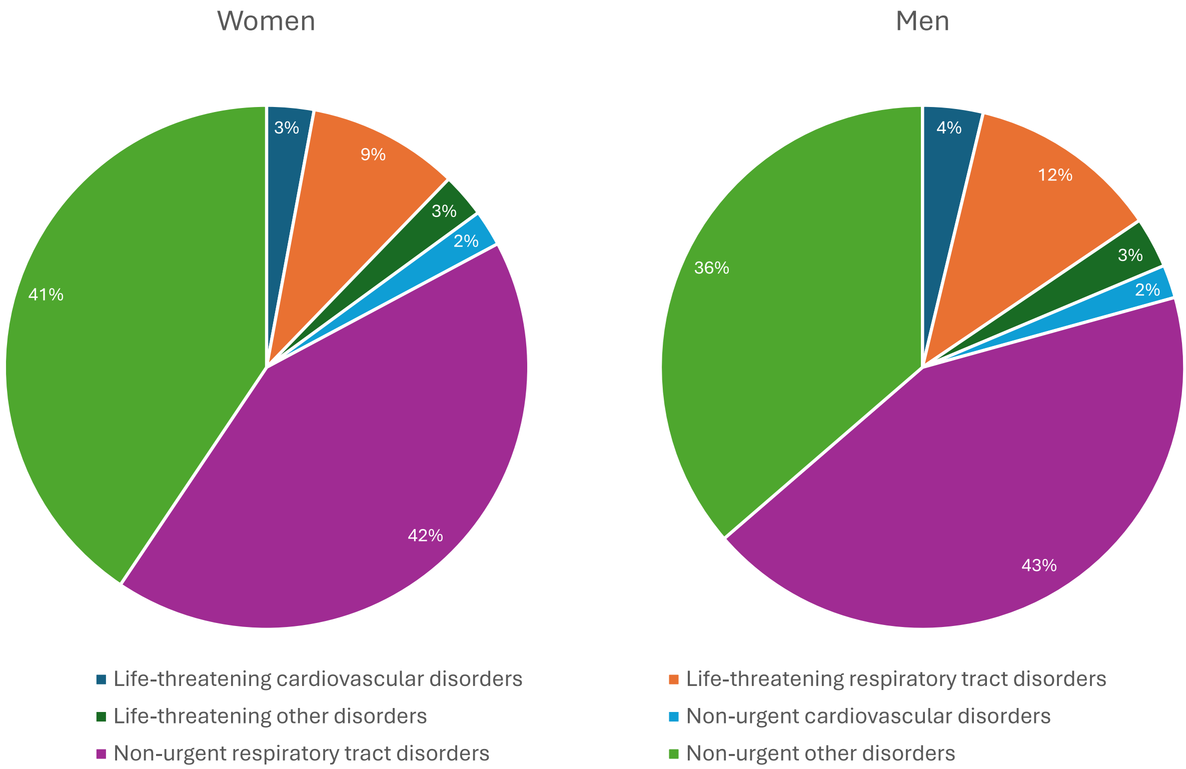

Fig. 2 Pie charts of final diagnostic categories of women and men calling OHS-PC with shortness of breath

men: 50.6% vs. 31.3%, $p=$ 0.001; p-value interaction term: 0.396) and more often used cardiovascular medication (women: 21.4% vs. 12.6%, $p=$ 0.003; men: 23.9% vs. 13.4%, $p=$ 0.001; p-value interaction term: 0.825). Gender-differences were not observed in medical history and medication use.

Symptoms

Women and men with LTEs were more often unable to speak full sentences (women: 42.2% vs. 10.3%, $p<$ 0.001 and men: 34.2% vs. 10.2%, $p<$ 0.001; p-value interaction term: 0.309). Gender-differences were not observed in symptoms.

Discussion

Summary

More women than men called OHS-PC because of SOB and women had a somewhat lower risk of LTEs than men. In both gender groups LTEs were not uncommon; among women 15.0%, and among men 18.7%, with a peak of 30% in women at the age of approximately 76 years and 27% in men at the age of approximately 77 years. Women had, compared to men more often an upper respiratory tract infection, unspecified chest pain and unspecified shortness of breath. Men had, compared to women, more often a severe COVID-19 infection, ACS, and SOB due to (existing) cancer.

We found no strong evidence of a difference in symptomatology between women and men experiencing an LTE amongst patients calling OHS-PC with SOB. We only found differences between women and men in two call characteristics: women with an LTE called relatively more often at night than women without an LTE, this was not apparent in men. GPs significantly more often participated in telephone triage of men who eventually showed to have an LTE, but not in women with an LTE.

Strengths and limitations

This is the first study comparing characteristics and symptoms between women and men with SOB calling the OHS-PC. We explicitly analysed whether variables predicted an LTE differently in women than in men. This study has unique data because we re-listened to the original triage conversations which gave us access to the callers'very initial symptom presentation. These data were collected without knowledge about the final diagnosis, thus avoiding hindsight bias. Finally, this information from the back-up tapes was linked to follow-up data from the patient's own GP, including hospital specialist letters if the patient was referred, for a reliable determination

Table 2 Characteristics of women and men calling OHS-PC with shortness of breath

Characteristics	Women $n = 1{,}030$ (55.3%)				Difference* (95% CI)	Men $n = 831$ (44.7%)				Difference* (95% CI)	*p*-value interaction term gender
	Total $n = 1{,}030$	LTE $n = 154$ (15.0%)	No LTE $n = 876$ (85.0%)	*p*-value		Total $n = 831$	LTE $n = 155$ (18.7%)	No LTE $n = 676$ (81.3%)	*p*-value		
Mean age in years (SD)	52.5 (22.0)	66.7 (18.7)	50.0 (21.6)	< 0.001[§]	16.8 (13.1 to 20.4)	54.4 (20.9)	62.8 (17.7)	52.5 (21.1)	< 0.001[§]	10.4 (6.8–13.9)	0.061[‖]
Call characteristics											
Call duration in min:sec (SD) (*n* = 1,843)**	11:53 (39:38)	13:54 (51:25)	11:32 (37:17)	0.498[§]	2:21 (−4:28 to 9:11)	14:02 (1:03:02)	10:31 (5:26)	14:56 (1:10:23)	0.438[§]	−4:24 (−15:33 to 6:44)	0.482[‖]
Calling at night (noon-8 AM)	170 (16.5%)	37 (24.0%)	133 (15.2%)	0.006[‡]	8.8 (1.6 to 16.0)	181 (21.8%)	29 (18.7%)	152 (22.5%)	0.300[‡]	3.8 (−3.1 to 10.7)	0.009[‖]
Someone else called on behalf of patient (*n* = 1,857)**	485 (47.2%)	108 (70.6%)	377 (43.1%)	< 0.001[‡]	27.5 (19.6 to 35.4)	462 (55.7%)	121 (78.1%)	341 (50.5%)	< 0.001[‡]	27.6 (20.1 to 35.1)	0.732[‖]
GP participated in triage (*n* = 1,856)**	509 (49.5%)	76 (49.4%)	433 (49.5%)	0.975[‡]	0.1 (−8.5 to 8.7)	376 (45.2%)	87 (56.1%)	289 (43.0%)	0.003[‡]	13.1 (4.4 to 21.8)	0.033[‖]
Medical history											
Cardiovascular disease (*n* = 920)**	164 (32.2%)	33 (55.9%)	131 (29.0%)	< 0.001[‡]	26.9 (13.6 to 40.2)	144 (35.1%)	41 (50.6%)	103 (31.3%)	0.001[‡]	19.3 (7.3 to 31.3)	0.396[‖]
Respiratory disease (*n* = 1,012)**	271 (47.3%)	41 (60.3%)	230 (45.5%)	0.022[‡]	14.8 (2.4 to 27.2)	204 (46.5%)	46 (52.9%)	158 (44.9%)	0.181[‡]	8.0 (−3.7 to 19.7)	0.439[‖]
Thromboembolic diseases (*n* = 660)**	16 (4.2%)	3 (9.7%)	13 (3.7%)	0.133[†]	6.0 (−4.6 to 16.6)	8 (2.9%)	2 (3.8%)	6 (2.6%)	0.645[†]	1.2 (−4.4 to 6.8)	0.557[‖]
Medication use											
Cardiovascular medication use	143 (13.9%)	33 (21.4%)	110 (12.6%)	0.003[‡]	8.8 (2.0 to 15.6)	127 (15.3%)	37 (23.9%)	90 (13.4%)	0.001[‡]	10.5 (3.3 to 17.7)	0.825[‖]
Respiratory medication use	280 (27.2%)	40 (26.0%)	240 (27.4%)	0.714[‡]	1.4 (−6.1 to 8.9)	188 (22.6%)	36 (23.2%)	152 (22.6%)	0.857[‡]	0.6 (−6.8 to 8.0)	0.702[‖]
Antithrombotic therapy	36 (3.5%)	8 (5.2%)	28 (3.2%)	0.231[†]	2.0 (1.9 to 2.1)	47 (5.7%)	18 (11.6%)	29 (4.3%)	< 0.001[‡]	7.3 (2.0 to 12.6)	0.274[‖]
Symptoms mentioned during the call											
Ankle oedema (*n* = 96)**	40 (65.6%)	7 (70.0%)	33 (64.7%)	1.000[†]	5.3 (−26.0 to 36.6)	14 (40.0%)	4 (57.1%)	10 (35.7%)	0.401[†]	21.4 (−19.3 to 62.1)	0.578[‖]

Table 2 (continued)

Characteristics	Women $n = 1,030$ (55.3%)				Difference* (95% CI)	Men $n = 831$ (44.7%)				Difference* (95% CI)	*p*-value interaction term gender
	Total $n = 1,030$	LTE $n = 154$ (15.0%)	No LTE $n = 876$ (85.0%)	*p*-value		Total $n = 831$	LTE $n = 155$ (18.7%)	No LTE $n = 676$ (81.3%)	*p*-value		
Anosmia (*n* = 100)**	27 (60.0%)	1 (50.0%)	26 (60.5%)	1.000†	10.5 (−60.3 to 81.3)	22 (40.0%)	0 (0.0%)	22 (42.3%)	0.267†	42.3 (28.9 to 55.7)	0.998$^{\Vert}$
Autonomic nervous system related symptoms*** (*n* = 1,373)**	383 (51.3%)	58 (54.7%)	325 (50.7%)	0.444‡	4.0 (−6.2 to 14.2)	312 (49.8%)	66 (56.9%)	246 (48.2%)	0.092‡	8.7 (−1.3 to 18.7)	0.527$^{\Vert}$
Coughing (*n* = 1,315)**	478 (65.4%)	77 (75.5%)	401 (63.8%)	0.021‡	11.7 (2.5 to 20.9)	416 (71.2%)	89 (77.4%)	327 (69.7%)	0.104‡	7.7 (−1.0 to 16.4)	0.636$^{\Vert}$
Coughing blood (*n* = 1,077)**	23 (3.8%)	5 (5.8%)	18 (3.5%)	0.355†	2.3 (−2.9 to 7.5)	25 (5.3%)	6 (6.7%)	19 (4.9%)	0.598†	1.8 (−3.8 to 7.4)	0.806$^{\Vert}$
Coughing sputum (*n* = 648)**	114 (30.7%)	15 (38.5%)	99 (29.8%)	0.268‡	8.7 (−7.3 to 24.7)	105 (37.9%)	22 (47.8%)	83 (35.9%)	0.129‡	11.9 (−3.8 to 27.6)	0.825$^{\Vert}$
Fever (*n* = 1,270)**	163 (22.8%)	28 (28.9%)	135 (21.8%)	0.123‡	7.1 (−2.5 to 16.7)	184 (33.2%)	47 (42.7%)	137 (30.9%)	0.018‡	11.8 (1.6 to 22.0)	0.672$^{\Vert}$
Malaise (*n* = 679)**	290 (79.0%)	46 (86.8%)	244 (77.7%)	0.148‡	9.1 (−1.1 to 19.3)	246 (78.8%)	58 (95.1%)	188 (74.9%)	< 0.001‡	20.2 (12.6 to 27.8)	0.097$^{\Vert}$
Musculoskeletal pain (*n* = 210)**	92 (82.1%)	4 (66.7%)	88 (83.0%)	0.291†	16.3 (−22.1 to 54.7)	77 (78.6%)	10 (90.9%)	67 (77.0%)	0.448‡	13.9 (−5.3 to 33.1)	0.158$^{\Vert}$
Palpitations (*n* = 157)**	57 (63.3%)	1 (20.0%)	56 (65.9%)	0.058†	45.9 (9.4 to 82.4)	42 (62.7%)	7 (63.6%)	35 (62.5%)	1.000‡	1.1 (−30.0 to 32.2)	0.116$^{\Vert}$
Rhinitis (*n* = 428)**	134 (56.8%)	11 (45.8%)	123 (58.0%)	0.253‡	12.2 (−8.8 to 33.2)	91 (47.4%)	9 (39.1%)	82 (48.5%)	0.397†	9.4 (−11.9 to 30.7)	0.863$^{\Vert}$
Throat complaints (*n* = 360)**	132 (63.2%)	14 (51.9%)	118 (64.8%)	0.192‡	12.9 (−7.2 to 33.0)	91 (60.3%)	8 (44.4%)	83 (62.4%)	0.199†	18.0 (−6.4 to 42.4)	0.769$^{\Vert}$
Tingling sensations (*n* = 104)**	40 (70.2%)	3 (100.0%)	37 (68.5%)	0.547†	31.5 (19.1 to 43.9)	30 (63.8%)	2 (100.0%)	28 (62.2%)	0.528†	37.8 (23.6 to 52.0)	1.000$^{\Vert}$
Chest pain characteristics											
Chest pain (*n* = 853)**	312 (63.7%)	30 (50.8%)	282 (65.4%)	0.029‡	14.6 (1.1 to 28.1)	191 (52.6%)	29 (43.3%)	162 (54.7%)	0.090‡	11.4 (−1.7 to 24.5)	0.712$^{\Vert}$

Table 2 (continued)

Characteristics	Women n = 1,030 (55.3%)				Difference* (95% CI)	Men n = 831 (44.7%)				Difference* (95% CI)	p-value interaction term gender
	Total n = 1,030	LTE n = 154 (15.0%)	No LTE n = 876 (85.0%)	p-value		Total n = 831	LTE n = 155 (18.7%)	No LTE n = 676 (81.3%)	p-value		
Chest pain when breathing (n = 169)**	84 (81.6%)	9 (90.0%)	75 (80.6%)	0.684†	9.4 (−10.9 to 29.7)	52 (78.8%)	7 (70.0%)	45 (80.4%)	0.431†	10.4 (−19.8 to 40.6)	0.317‖
Pain onset < 12 h (n = 293)**	100 (55.6%)	7 (50.0%)	93 (56.0%)	0.782†	6.0 (−21.3 to 33.3)	65 (57.5%)	6 (46.2%)	59 (59.0%)	0.390†	12.8 (−16.0 to 41.6)	0.734‖
Pain duration > 15 min (n = 251)**	145 (94.8%)	10 (83.3%)	135 (95.7%)	0.121‡	12.4 (−8.9 to 33.7)	95 (96.9%)	11 (100.0%)	84 (96.6%)	1.000‡	3.4 (−0.4 to 7.2)	0.999‖
Radiation of pain (n = 220)**	86 (64.7%)	8 (53.3%)	78 (66.1%)	0.393†	12.8 (−13.9 to 39.5)	42 (48.3%)	6 (50.0%)	36 (48.0%)	1.000†	2.0 (−28.5 to 32.5)	0.460‖
Severe pain (score > 7 on VAS) (n = 100)**	19 (29.7%)	3 (60.0%)	16 (27.1%)	0.150†	32.9 (−11.5 to 77.3)	8 (22.2%)	1 (25.0%)	7 (21.9%)	1.000†	3.1 (−41.7 to 47.9)	0.434‖
Shortness of breath characteristics											
Stridor (n = 1,147)**	28 (4.4%)	3 (3.7%)	25 (4.5%)	1.000†	0.8 (−3.7 to 5.3)	10 (2.0%)	1 (1.1%)	9 (2.2%)	0.697†	1.1 (−1.4 to 3.6)	0.663‖
Unable to speak full sentences (n = 1,528)**	126 (14.6%)	49 (42.2%)	77 (10.3%)	< 0.001‡	31.9 (22.6 to 41.2)	97 (14.5%)	41 (34.2%)	56 (10.2%)	< 0.001‡	24.0 (15.1 to 32.9)	0.309‖
Wheezing (n = 1,211)**	89 (13.2%)	19 (21.1%)	70 (12.0%)	0.018‡	9.1 (0.3 to 17.9)	90 (16.7%)	20 (19.6%)	70 (16.0%)	0.381‡	3.6 (−4.8 to 12.0)	0.290‖

GP General practitioner, *OHS-PC* Out-of-hours primary care, *SOB* Shortness of breath, *VAS* Visual Analogue Scale

* Mean difference for continuous variables and risk proportion difference for categorical variables

** For these variables there were missing data

*** Autonomic nervous system related symptoms consist of one or more of the following: nausea and/or vomiting, sweating, pallor/ashen skin, (near) collapse

† Fisher's exact test,

‡ Pearson's chi-square test

§ independent sample T-test

|| logistic regression analysis with interaction term between gender and variable

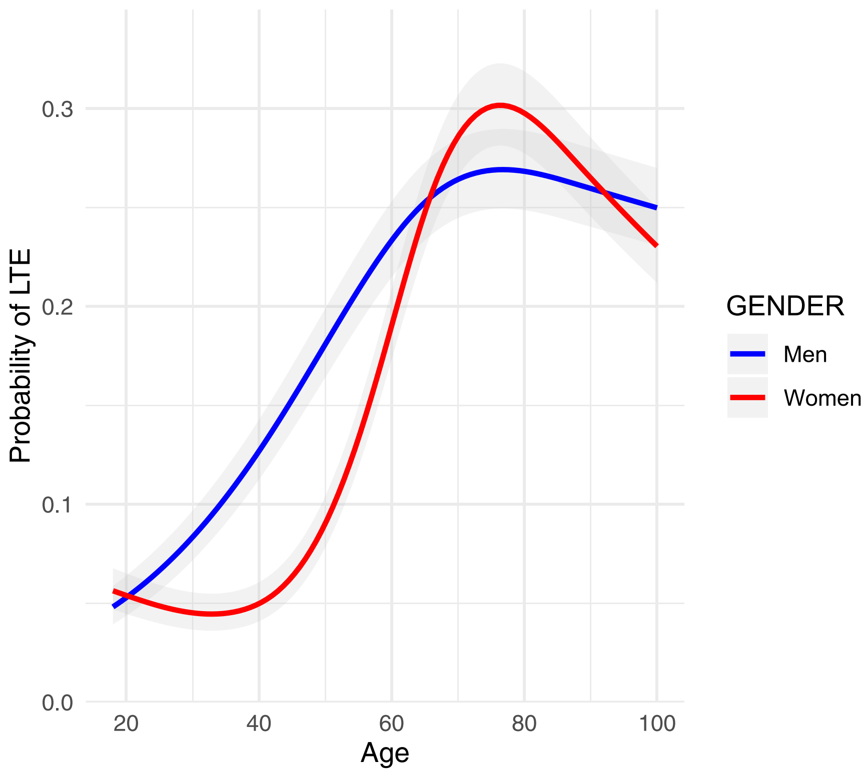

Fig. 3 Logistic regression model with age and gender for predicting diagnosis life-threatening event

of the final diagnosis up to 30 days after the contact with OHS-PC.

We were able to include patients without strict exclusion criteria, making our study population representative of the real-life situation. Our findings are therefore most likely generalisable to other countries with similar OHS-PC services, including the United Kingdom, Germany, Scandinavian countries, and possibly other European countries. [38].

A notable limitation is that there were missing values for all symptoms, particularly symptoms not included in the NTS entrance complaint SOB. Missing data is common when using routine care data. However, we do not expect there to be an association between missing information and the occurrence/absence of life-threatening conditions (missing at random), so this presumably did not affect our primary outcome.

A further limitation is that our study period coincided with the COVID-19 pandemic, which impacted the prevalence of LTEs in both genders; 4.7% of women and 7.6% of men had a severe COVID-19 infection, and 21.2% a mild or moderate COVID-19 infection. When excluding the COVID-19 cases from our analysis (both mild or moderate and severe COVID-19), the prevalence of LTEs decreases in both genders: 13.8% in women and 15.7% in men. This should be taken into consideration in the interpretation of our findings as this could make our study population less representative of the current real-life patient population. However, to date, there is no evidence that those with an LTE other than severe COVID-19 presented with other symptoms during the pandemic, independent of any concomitant COVID-19 infection, so the effect on the primary outcome seems limited.

Another limitation was that we could not include 3,333 patients due to general practitioners being unwilling or unable to provide follow-up information on final diagnosis. Although this is a substantial proportion of the initial sample, it is unlikely that this led to significant selection bias. Patient and call characteristics were generally comparable between those with and without follow-up data. Furthermore, general practitioners' willingness or ability to provide follow-up information is unlikely associated with the presence of LTEs in individual cases.

Finally, we had to exclude 7.5% of eligible triage conversations due to unavailability of call recordings or a triage conversation in another language than Dutch or English. We could, however, show that age and gender did not significantly differ between those with and without an available call recording. Thus, this selection did likely not cause selection bias, the more so because the availability of triage conversations seems not to be associated with the medical outcome of individual callers.

Comparison with existing literature

Two studies performed in the Belgian and German daytime GP setting also reported that women more often contacted their GP for acute SOB than men. [39, 40].

We found that the risk of LTEs was lower in women with SOB than men, similar to the aforementioned Belgian study; men with SOB had a higher risk of immediate referral, hospitalization, and death than women. [40] Albeit the study did not report on the final diagnosis, this suggests that men were more likely to have an urgent underlying medical condition. The Belgian authors speculated that this outcome could be attributed to smoking-related medical conditions, e.g., COPD, lung cancer and cardiovascular diseases which are more common in men. We found that men more often had ACS and SOB due to (existing) cancer, but we could not detect gender-related differences for COPD exacerbations. Our observation that ACS is more common in men is also reported in other studies. [41–43] Also in line with previous studies and summarized in a systematic review is our finding that severe COVID-19 infections were more common in men than women. [44].

Although undetected severe underlying conditions seem uncommon, this might occur more in women. [45] Previous studies in daytime primary care showed that women with symptoms suggestive of respiratory diseases or coronary heart diseases were less likely to be referred for further diagnostic work-up and had more often unspecified diagnoses, which could potentially be missed LTEs. [46, 47] In our study women were also more often diagnosed with unspecified SOB or unspecified chest pain than men. We tried to reduce the risk of missing an LTE by counting any LTE occurring within 30 days of follow-up period. Suggestions posed in previous studies as explanation that women more often received an unspecified diagnosis than men are that women more often seek healthcare and have a less straightforward way of presenting their symptoms. [24, 46] We did indeed find that more women than men contacted OHS-PC for SOB. However, we do not know the ratio of men to women among patients with SOB in the overall population. Consequently, it is impossible to say whether women with SOB call the OHS PC relatively more often, as often or less often than men with SOB. We did not find differences between both genders regarding symptoms.

Similarly, the same symptoms were helpful to differentiate ACS from no ACS in women and men, as we have found in two studies in OHS-PC among patients with chest discomfort suspected of having an ACS. [48, 49] The first study among 518 callers with chest discomfort reported that stabbing pain was associated more with the absence of ACS in men than in women. In men radiation of chest pain was associated more with ACS than in women. However, interaction terms for these observations were not reported which hampers interpretation. [49] The second study among 1,795 callers to the OHS-PC with chest discomfort found that among the 29 analysed characteristics, only radiation to the jaws and pain severity showed gender-related differences. Radiation to the jaws was discriminative among men for ACS, and severe chest pain among women. [48] Also other studies executed in emergency departments in the United States, Australia and New Zealand reported that there were more similarities than differences between the symptoms associated with ACS in women and men who presented with a possible ACS. [50, 51] However, numerous studies and systematic reviews compared the symptoms of women and men with ACS with each other, and then, there are substantial differences in prevalence of certain symptoms. [52] However, these differences are not useful for triage or for the clinician to come to a diagnosis. For example, women with ACS are more likely to report dizziness than men with ACS. Similarly, women with suspected symptoms of ACS, but not diagnosed with ACS, also commonly experience dizziness compared to men without an ACS diagnosis. Thus, differences in symptoms between women and men diagnosed with ACS are not helpful for triage where you want to discriminate women with ACS from women with suspected symptoms but without ACS. This also applies for men. This is consistent with our findings, well within a different domain, e.g., patients with SOB, as we found no strong evidence for any gender-related difference in symptomatology associated with LTEs.

We found that the risk of an LTE increased when women called at night while this was not observed in men. Remarkably, in another Dutch study of our group among 1,655 patients calling OHS-PC with chest discomfort the relation was more or less the other way around; for men calling at night the odds ratio (OR) of having an ACS was 2.33 (95% CI: 1.68–3.22), while in women the OR was 1.29 (95% CI: 0.83–1.99). [53] The difference between our study and the previous study could possibly be explained by differences in main symptom (SOB vs. chest discomfort) and differences in LTEs (multiple cardiac and pulmonary diseases vs. ACS). In our population in whom SOB was chosen as entrance complaint by the triage nurse, only 0.7% of patients had an ACS (0.3% in women and 1.2% in men), while in the study of Wouters et al. ACS occurred in 12.0% (8.9% in women and 15.9% in men).

Implications for research and/or practice

Our findings suggest that similar symptoms are associated with LTEs in both women and men calling OHS-PC with SOB. It is however worth noting that the lack of evidence for interactions does not necessarily mean that significant differences between men and women do not exist. This is because detecting interactions often requires larger sample sizes than those needed for detecting main effects. [54] However, looking at the point estimates and the direction of differences between LTEs and non-LTEs in women versus men, it is unlikely that a difference would have been found for most variables in a larger dataset. Future studies with larger cohorts could provide more clarity on potential gender-based differences in symptom presentation and outcomes.

As men had a higher chance of an LTE than women, gender itself might be a crucial factor to discriminate patients with and without LTEs. Multivariable analyses are, however, needed to further investigate the importance of this factor among other factors which could optimize telephone triage in callers with SOB. Age is another important factor to consider in both women and men, however, somewhat differently. Below the age of 40 the risk of an LTE is low with 5% in women followed by a steep increase between 40 and 70 years to around 30% till the age of 80. In men, there is a gradual increase in risk of LTE from 5% at the age of 20 till 27% at the age of 75 years. Based on this study, other potential candidate predictors for this multivariable model might include someone else calling on behalf of the patient, a history of cardiovascular disease, use of cardiovascular medication and the inability to speak full sentences.

Among the two differences observed in call characteristics, calling at night seems most promising for adoption into practice. However, this necessitates further confirmation before eventual implementation.

Conclusions

Amongst patients contacting OHS-PC with SOB about 1 in 6 had an LTE, men somewhat more than women. We found no strong evidence of gender-related differences in symptomatology associated with LTEs. Women but not men had an increased risk of LTE during night-time.

Abbreviations

ACS	Acute coronary syndrome
CI	Confidence interval
EHR	Electronic health records
GP	General practitioner
LTE	Life-threatening event
NTS	Netherlands Triage Standard
OHS-PC	Out-of-hours primary care
OR	Odds ratio
RR	Relative risk
SD	Standard deviation
SOB	Shortness of breath

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Authors' contributions

FR, GJG, DZ and RPV are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, GJG, DZ and RPV. MS, AD and MD conducted data acquisition. MS and GR performed the analyses and wrote the first draft of the manuscript, under supervision of RPV. EdG, GJG, MvS, AD, MD, FR, DZ and RPV provided intellectual input and critically revised the manuscript. All approved the last version of the manuscript.

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Data availability

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.

Declarations

Ethics approval and consent to participate

Our study protocol has been reviewed by the Medical Ethics Committee (MREC) Utrecht (reference number 21/361). The MREC concluded that this study is not within the scope of the WMO and granted an exemption for this study. We used a waiver for informed consent (this exception to the informed consent has been described in The Declaration of Helsinki and is further specified in the CIOMS guideline which contains a part about waiving informed consent). Personal data and research data was de-identified according to the European General Data Protection Regulation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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