Sex differences in the trajectories to diagnosis of patients presenting with common somatic symptoms in primary care: an observational cohort study

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ABSTRACT

Objective: Little insight exists into sex differences in diagnostic trajectories for common somatic symptoms. This study aims to quantify sex differences in the provided primary care diagnostic interventions for common somatic symptoms, as well as the consequences hereof for final diagnoses.

Methods: In this observational cohort study, we used real-world clinical data from the Dutch Family Medicine Network (N = 34,268 episodes of care related to common somatic symptoms; 61.4% female). The association between patients’ sex on the one hand, and diagnostic interventions and disease diagnoses on the other hand, were assessed using multilevel multiple logistic regression analyses. Structural equation modelling was used to estimate a mediation model with multiple parallel mediators to assess whether the fewer disease diagnoses given to female patients were mediated by the fewer diagnostic interventions female patients receive, compared to male patients.

Results: Women received fewer physical examinations (OR = 0.84, 95%CI = 0.79–0.89), diagnostic imaging (OR = 0.92, 95%CI = 0.84–0.99) and specialist referrals (OR = 0.85, 95%CI = 0.79–0.91) than men, but more laboratory diagnostics (OR = 1.27, 95%CI = 1.19–1.35). Women received disease diagnoses less often than men for their common somatic symptoms (OR = 0.94, 95%CI = 0.89–0.98). Mediation analysis showed that the fewer disease diagnosis in female patients were mediated by the fewer diagnostic interventions conducted in women compared to men.

Conclusion: This study shows that sex inequalities are present in primary care diagnostic trajectories of patients with common somatic symptoms and that these lead to unequal health outcomes in terms of diagnoses between women and men. FPs have to be aware of these inequalities to ensure equal high-quality care for all patients.

1. Introduction

Health outcomes are closely related to patients’ trajectories to diagnosis [1]. A diagnostic trajectory comprises everything a family physician (FP) does, including diagnostic interventions, to obtain a diagnosis for a patient’s complaint. Yet, patients’ characteristics, including their sex, may influence the FPs perception of symptoms and consequently, patients’ diagnostic trajectories [1].

Diagnostic trajectories for multiple diseases differ between women and men. A recent study shows that women receive fewer physical examinations, diagnostic imaging and specialist referrals when they present with cough and/or dyspnoea in primary care than men [2]. Additionally, studies show that a patient’s sex is associated with different diagnostic trajectories in coronary heart disease (CHD). Women presenting with symptoms suggestive of CHD in primary care are less likely to receive physical examinations [3,4]. A similar sex difference is observed in colorectal cancer, as studies show women have higher mortality rates and are less often screened than men [5]. However, a recent study shows that men are less likely to receive an early diagnosis of dementia than women [6].

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Although sex differences in the prevalence and longevity of common somatic symptoms are recognized [7,8], little insight exists into sex differences in the primary care diagnostic trajectories related to these symptoms. Most research into diagnostic trajectories focuses on previously diagnosed disease [9,10] and only the aforementioned study on respiratory symptoms studied diagnostic trajectories from symptom presentation to final diagnosis in primary care [2]. Additionally, previous research into diagnostic trajectories is based on self-reported outcomes, which are prone to recall bias [11,12].

It is thought that sex differences exist in whether patients receive a disease diagnosis [13,14], with women’s symptoms remaining more often unexplained than men’s. However, it remains unknown whether the primary care diagnostic trajectory associates with symptoms that remain unexplained. It is pivotal to understand sex differences in diagnostic trajectories of somatic symptoms as these may result in sex inequalities in healthcare and sex-skewed morbidity or mortality rates [5,15].

Therefore, this study aims to quantify sex differences in primary care diagnostic trajectories of patients with common somatic symptoms and to assess whether potential sex differences in these trajectories are associated with whether the somatic symptoms are ultimately attributable to a disease (i.e. disease diagnosis) or continue to be symptoms that cannot be (fully) explained by an underlying disease or bodily abnormality (i.e. symptom diagnosis) [16]. Firstly, we will study the presence of differences between female and male patients in provided diagnostic interventions when a patient presents with somatic symptoms in primary care. Secondly, we will assess whether sex differences exist in whether the patient receives a disease diagnosis when presenting with somatic symptoms. Lastly, we will study whether potential differences in women’s and men’s diagnostic trajectories are associated with patients’ final diagnoses.

2. Methods

2.1. Study design and data collection

In this observational cohort study we used data from the Practice Based Research Network (PBRN) Family Medicine Network (FaMe-Net), which includes approximately 32,000 patients and 26 FPs in seven different primary care practices throughout the Netherlands. Studies involving FaMe-Net data are exempted from ethical review by the CCMO (Dutch Central Committee on research involving human subjects). Patients are extensively informed about the inclusion of their health-related information in FaMe-Net, and are offered the opportunity to opt out of FaMe-Net. FaMe-net is embedded in the regular Dutch primary care system. It is the world’s oldest PBRN and since its inception patients’ morbidity is systematically registered within an episode of care (EoC) structure [17]. An EoC is defined as a patient’s health problem from the first encounter until the last encounter related to that specific health problem. Within each encounter of an EoC, the FP routinely and systematically codes the patient’s reason for encounter (RFE), diagnosis and interventions (including physical examinations, diagnostic tests and referrals to specialists) according to the International Classification of Primary Care (ICPC-2). An EoC may start with more than one RFE, but one final diagnosis is ultimately linked to all encounters within the EoC. The registered diagnosis of an EoC can be modified anytime when new insights regarding the patient’s RFE arise. The RFE should be acknowledged by the patient as a correct description of their demand of care. The validity of data registration is high, as participating FPs are extensively informed about the inclusion of their health-involving FaMe-Net data are exempted from ethical review by the CCMO (Dutch Central Committee on research involving human subjects). Patients presented common somatic symptoms, we conducted multilevel multiple logistic regression analyses. Patients’ sex, patients’ age at time of diagnosis, the number of contacts between patients and FPs during an EoC, the type of RFE, the type of consultations (face-to-face or by phone/ electronic) and the presence of comorbidities at the start of an EoC (Supplementary Table 1) were included as independent variables; the diagnostic interventions were included as dependent variable. As EoCs are nested at the individual level, analyses were clustered at this level. To exclude that the association between sex and laboratory diagnostics was explained by women receiving laboratory diagnostics to confirm a urinary tract infection when presenting (lower) back pain, we conducted a sensitivity analyses in which EoCs starting with (lower) back pain were excluded. We included sex-by-RFE interaction terms to assess whether the association between the type of RFE and interventions differed between female and male patients.

Similar analyses, with disease diagnosis as the outcome, were conducted to assess whether the presence of disease diagnoses in an EoC that started with somatic symptoms differed between women and men. A disease diagnosis was operationalized as ICPC≥70, including psychiatric ICPC codes. This means that symptoms, followed over time, evolved in a diagnosed disease. In contrast, a symptom diagnosis was operationalized as ICPC≤30, in which symptoms followed over time continued to be symptoms as relevant diagnostic criteria were not met. For example, a symptom diagnosis is registered for symptoms if during the whole year no medical diagnosis (i.e. an ICPC≥70) has been registered as explanation for the symptom.

To assess whether the diagnostic interventions mediated the association between sex and disease diagnosis, we used structural equation modelling to estimate a mediation model with multiple parallel mediators. We used weighted least-squares-estimation with 1000 bootstraps. Because all involved variables were binary, we used a probit link function to estimate all regression coefficients and 95% CIs for direct and indirect paths between sex and final diagnosis. To facilitate easier interpretation of the probit slopes, we converted the predicted probabilities of the probit model to odds and computed the concomitant odds ratio [20,21].

To test whether continuous covariates included in the logistic regression analyses fulfilled the linearity assumption of multiple logistic regression we divided the covariates into categories, and assessed whether the estimates changed monotonically. We found no indication for multicollinearity as the VIF was <5 in all analyses [22]. The statistical analyses and additional descriptive analyses were conducted in IBM SPSS Statistics v. 25, except for the mediation analysis, which was performed in R version 3.5.1, package ‘Lavaan’ version 0.6–5 [23]. We
maintained a two-sided alpha-value of \( p < 0.004 \) corrected for multiple testing.

3. Results

3.1. Study population and incidence rates of common somatic symptoms

We identified 34,268 unique Er of that started with 46,898 RFEs. In total, 9690 (28.3%) ErC started with more than one RFE. An overview of the study population is given in Table 1.

Fig. 1 shows that heart pain and chills were equally presented by women and men; other symptoms were more frequently presented by women than men. The most prevalent symptoms in both sexes were weakness/general tiredness, (lower) back pain, swallowing/throat symptoms, and arm or leg symptoms. In total, 21,031 (61.4%) female ErC and 13,327 (38.6%) male ErC were found, translating into a total of 266.4 (95%CI = 263.3–269.5) and 174.8 (95%CI = 172.1–177.5) ErC related to somatic symptoms per 1000 patient years in women and men, respectively (Supplementary Table 2).

3.2. Sex differences in diagnostic interventions

Table 2 shows that women have 0.84 (95%CI = 0.79–0.89) times the odds of men to receive a physical examination during their ErC, adjusted for age, number of contacts within an ErC, type of consult and RFE, and comorbidities. Also, female patients received fewer diagnostic imaging and specialist referrals than their male counterparts. In contrast, we found that women were more likely to receive laboratory diagnostics than men (OR = 1.27, 95%CI = 1.19–1.35). We found an unadjusted OR of 1.28 (95%CI = 1.21–1.35) and an adjusted OR of 1.20 (95%CI = 1.12–1.28) in sensitivity analyses that excluded ErC related to (lower) back pain.

In models in which we included sex-by-RFE interaction terms we found that the associations between the type of RFE and diagnostic interventions or a specialist referral did not differ between women and men. However, a significant interaction term (OR = 1.33, 95%CI = 0.13–0.81) showed that women were less likely to receive a physical examination when presenting chills. Moreover, significant interaction terms showed that women were more likely to receive laboratory diagnostics if they presented with vertigo/dizziness, (lower) back pain and weakness/general tiredness than men (OR = 1.91, 95%CI = 1.43–2.56; OR = 1.69, 95%CI = 1.26–2.26; OR = 1.46, 95%CI = 1.14–1.88, respectively). Analyses stratified per RFE are shown in Supplementary Table 3.

Table 1 Overview of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N (%)</td>
<td>10,541</td>
<td>7915 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Patient years(^a), N (%)</td>
<td>78,954</td>
<td>75,734 (52.3) (47.7)</td>
<td></td>
</tr>
<tr>
<td>New ErC, N (%)</td>
<td>21,031</td>
<td>13,327 (61.4) (38.6)</td>
<td></td>
</tr>
<tr>
<td>Age in years, Mean (SD)</td>
<td>43.4 (23.1)</td>
<td>42.3 (23.9)</td>
<td>&lt;0.001(^b)</td>
</tr>
<tr>
<td>Number of encounters per ErC, Median (IQR)</td>
<td>1.0 (1.0), 1.0 (1.0)</td>
<td>0.053(^c)</td>
<td></td>
</tr>
<tr>
<td>ErC with comorbidities at the start, N (%)</td>
<td>8282 (39.4)</td>
<td>5295 (43.7)</td>
<td>0.271(^d)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>5741 (27.3)</td>
<td>3827 (28.9)</td>
<td>0.001(^e)</td>
</tr>
<tr>
<td>Asthma and/or COPD</td>
<td>3106 (14.8)</td>
<td>1998 (15.1)</td>
<td>0.427(^f)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1684 (8.0)</td>
<td>979 (7.4)</td>
<td>0.038(^g)</td>
</tr>
</tbody>
</table>

\(^a\) The cumulative years the included patients were at risk for an incident common somatic symptom.
\(^b\) Independent t-test;
\(^c\) Mann-Whitney U test;
\(^d\) Chi-Square test

3.3. Sex differences in final diagnoses

Table 3 shows that women have 0.94 times the odds (95%CI = 0.89–0.98) of men to receive a disease diagnosis, when they present with somatic symptoms in primary care, adjusted for their age, number of contacts within an ErC, type of consult and RFE and comorbidities. In heart pain we found the largest sex difference in receiving a disease diagnosis as final diagnosis: women had 0.56 times the odds (95%CI = 0.37–0.84) compared to men to receive a disease diagnoses. Supplementary Table 4 provides the sex-stratified final diagnoses most commonly given for somatic symptoms.

3.4. Mediation effects of interventions on the association between sex and disease diagnoses

Table 4 shows that the association between sex and disease diagnoses (i.e. the direct effect) is no longer statistically significant (OR = 1.02; 95%CI = 0.99–1.06), whereas the total effect was statistically significant (OR = 0.94; 95%CI = 0.93–0.98). Diagnostic interventions, except for diagnostic imaging, at least partly explain the association between sex and final diagnosis. Supplementary Fig. 5 shows the probit regression coefficients.

4. Discussion

This study identified sex differences in the diagnostic trajectories of patients presenting with somatic symptoms in primary care. We found that women present themselves more often with somatic symptoms than men, and that men are more likely to receive a physical examination, diagnostic imaging and specialist referrals than women, whereas women received more laboratory diagnostics. This is the first study that shows that the fewer disease diagnoses given to women are mediated by the fewer diagnostic interventions that are performed in women.

4.1. Strengths and limitations

Our study had several strengths. First, the FaMe-Net database holds rich, valid and accurate primary care data of a large patient cohort. Participating FPs frequently discuss coding and the inherent warning system in the FP information system resulted in no indication of missing data in our cohort. Additionally, we used the RFE to define symptoms, which is an accurate measure, as the RFE is not interpreted by the FP [24].

We acknowledge several limitations of our study as well. First, the patients’ full medical history was unknown to the researchers. Second, the adjustment for comorbidities included cardiovascular diseases, respiratory diseases and malignancies, which is non-exhaustive. Both the patient’s full medical history and comorbidities could have affected FPs’ clinical decision making process and final diagnosis. Further research should investigate whether FPs value medical history and comorbidities similarly in female and male patients. Also, we could not include possible effect modifiers in our analyses, for example the patient’s socioeconomic status or ethnicity, and the FP’s working experience and so [25], as these data were unavailable.

Notably, especially the FP-patient sex concordance is important in patients’ diagnostic trajectories. For example, female physicians are more inclined to deliver female preventive procedures, such as a Papsmear [25,26]. Patients, irrespective their sex, are also more assertive and demanding towards female FPs than towards male FPs. Therefore, patients may request more interventions from female FPs [27]. Thus, if more female than male FPs are included in our study, the results may be skewed towards more diagnostic interventions, especially in female patients.
management of CHD found similar sex differences in the conduct of nosis imaging and specialist referrals than men when presenting with diagnostic trajectories in primary care for respiratory complaints: this care. Our results are in line with a recent study that assessed patients diagnostics, when presenting common somatic symptoms in primary women to receive fewer diagnostic interventions, except for laboratory matic symptoms in primary care than men [28, 29]. We also found-

4.2. Comparison with existing literature

In line with previous studies, we found women to present more so-
matic symptoms in primary care than men [28, 29]. We also found women to receive fewer diagnostic interventions, except for laboratory diagnostics, when presenting common somatic symptoms in primary care. Our results are in line with a recent study that assessed patients’ diagnostic trajectories in primary care for respiratory complaints: this study found that women receive fewer physical examinations, diagnostic imaging and specialist referrals than men when presenting with cough and/or dyspnoea [2]. Additionally, previous studies assessing the management of CHD found similar sex differences in the conduct of physical examinations and specialist referrals [4, 20, 31]. One study, in contrast, found a higher diagnostic test ordering in primary care in men for CHD-related symptoms [3]. However, this study did not distinguish between diagnostic imaging and laboratory diagnostics.

Our finding that women are more often diagnosed with a symptom diagnosis than men is in line with earlier literature [32]: a previous study found that women have 0.82 (95% CI = 0.74–0.88) times the odds of men to receive a disease diagnosis for their somatic symptoms [1]. The difference in strength of the association between female sex and a disease diagnosis compared to the current study may be partly due to the different symptoms that were assessed in the previous study. The

\[
\text{Women} \quad \text{Men} \quad \text{Number of EoC} (\%) \quad \text{OR (95%CI)}^a
\]

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of EoC (%)</th>
<th>Female EoC</th>
<th>Male EoC</th>
<th>Unadjusted</th>
<th>Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>16,052</td>
<td>10,876</td>
<td>0.79</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Laboratory diagnostics</td>
<td>5649</td>
<td>2875</td>
<td>1.33</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>Diagnostic imaging</td>
<td>1264 (6.0)</td>
<td>951 (7.2)</td>
<td>0.83</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Specialist referrals</td>
<td>2160</td>
<td>1611</td>
<td>0.83</td>
<td>0.85</td>
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</tr>
</tbody>
</table>

a Odds ratios reflect women compared to men.
b Adjusted for the patients’ age at time of diagnosis, number of contacts in an EoC, presence of comorbidities at the start of an EoC, type of consult and the type of RFE.

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\]

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<th>Male EoC</th>
<th>Unadjusted</th>
<th>Adjustedb</th>
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</tr>
</tbody>
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a Odds ratios reflect women compared to men.
b Adjusted for the patients’ age at time of diagnosis, number of contacts in an EoC, presence of comorbidities at the start of an EoC, type of consult.
c Adjusted for aforementioned factors and type of RFE as well.

previous study included, for example, constipation and sleep distur-
bances, whereas the current study did not include these symptoms. Similarly, a recent study found an incidence rate ratio of 0.70 (95% CI = 0.54–0.91) for receiving a disease diagnosis for somatic symptoms in

\[
\text{Women} \quad \text{Men} \quad \text{EoC with disease} \quad \text{diagnoses, N (%) OR (95%CI)}^a
\]

<table>
<thead>
<tr>
<th>RFE</th>
<th>Female EoC</th>
<th>Male EoC</th>
<th>Unadjusted</th>
<th>Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>858</td>
<td>506</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Dizziness</td>
<td>629</td>
<td>365</td>
<td>0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>Heart pain</td>
<td>60 (17.8)</td>
<td>93</td>
<td>0.54</td>
<td>0.56</td>
</tr>
<tr>
<td>Nausea</td>
<td>295</td>
<td>114</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>50 (15.5)</td>
<td>51</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1240</td>
<td>933</td>
<td>0.87</td>
<td>0.92</td>
</tr>
<tr>
<td>Chills</td>
<td>35 (52.2)</td>
<td>40</td>
<td>0.68</td>
<td>0.71</td>
</tr>
<tr>
<td>Tingling fingers, feet and/or toes</td>
<td>149</td>
<td>101</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>Swallowing/throat symptoms</td>
<td>1821</td>
<td>1108</td>
<td>1.11</td>
<td>1.21</td>
</tr>
<tr>
<td>Weakness/general tiredness</td>
<td>18.9 (23.0)</td>
<td>0.78</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Arm and/or leg symptoms</td>
<td>1039</td>
<td>813</td>
<td>0.91</td>
<td>0.89</td>
</tr>
</tbody>
</table>

a Odds ratios reflect women receiving a disease diagnosis (either psychiatric or somatic) compared to men.
b Adjusted for the patients’ age at time of diagnosis, number of contacts in an EoC, presence of comorbidities at the start of an EoC, type of consult.
c Adjusted for aforementioned factors and type of RFE as well.
women compared to men in a Latino and Asian American patient population [33]. Possibly, ethnic diversity interacts with sex, resulting in an excess of symptom diagnoses in women.

It is argued that many factors interact and form a complex interplay that could partially explain the sex differences we found in interventions and final diagnoses. First, it is known that women report more numerous and varied somatic symptoms [7,34], possibly due to biological sex differences in the central processing of sensory information [35].

Second, women visit their FP more often and earlier in their symptom trajectory than men [36]. The heightened bodily vigilance of women and their familiarization with primary care is thought to lower the threshold of seeking care for somatic symptoms [37,38]. In contrast, masculine gender stereotypes, for example stoicism about symptom reporting [28,39], may delay male healthcare-seeking behaviour. Due to the relatively early female healthcare-seeking behaviour, women present with less typical symptoms of disease and consequently receive fewer specialist referrals and diagnoses.

Third, sex differences in communication styles could contribute to the sex difference in performed diagnostic interventions: women’s communication is more subjective, talkative and polite, whereas men’s communication is thought to be more demanding, rational and straightforward [40].

Fourth, we found that women receive more laboratory diagnostics. The higher likelihood of requesting laboratory diagnostics for female patients could be an attempt to reassure the patient, as uncertainty about symptoms is more often reported in women [3,41,42]. However, FPs also request laboratory diagnostic tests to mitigate their own diagnostic uncertainty [43,44], which is thought to be higher in female patients. Notably, sex differences in diagnostic uncertainty are mainly investigated for CHD-related symptoms [3,45]; to our knowledge no studies investigated sex differences in diagnostic uncertainty in common somatic symptoms. Additionally, laboratory diagnostics are an easily conducted and accessible intervention to rule out underlying conditions related to common somatic symptoms that are more frequent in women, for example urinary tract infections and anaemia.

Last, FPs’ prejudices could also promote sex differences in diagnostic trajectories. For example, it is argued that physicians more readily assume somatization in women [46] and offer fewer interventions to women. FPs’ state that they feel that their unconscious presumptions about gender and sex affect their clinical decision making process in a way that may disadvantage one sex over the other [37].

4.3. Conclusions and implications for research and practice

This study shows that sex inequalities exist in the diagnostic trajectories of patients presenting somatic symptoms in primary care. However, it remains unknown whether these inequalities are justified. Although we used men as reference category in our analyses, male diagnostic trajectories are not necessarily the golden standard: possibly males are overmedicalized in comparison to females. The sex differences in diagnostic interventions may also be due to a differing probability for final diagnoses between women and men. Men receive disease diagnoses more frequently than women. On the one hand, this could be attributable to a higher detection rate of diseases in men as they receive more diagnostic interventions. Ultimately, this may be a vicious circle: increased use of diagnostic interventions in male patients leads to a higher detection rate of diseases in men compared to women. Consequently, the male rate of disease diagnoses increases, followed by an increased probability of FPs ordering more diagnostic interventions, as FPs base their actions on guidelines and personal experience. On the other hand, men may have a truly higher a priori chance of underlying disease than women when consulting the FP for somatic symptoms, which justifies the sex difference in diagnostic interventions. Therefore, further research could focus on whether women and men equally benefit from diagnostic interventions. Additionally, an experimental vignette-based study in which the vignette differs in patient’s sex that asks FPs to suggest diagnostic interventions for the patient with a common somatic symptom may provide insights into sex differences, and reasons behind these, in diagnostic interventions suggested by FPs [47].

Clinically this study suggest that the fewer diagnostic interventions in women may result in fewer disease diagnoses. Thus, if additional research shows that men and women equally benefit from diagnostic interventions in terms of receiving a disease diagnosis, FPs should be aware of the negative impact of the underuse of diagnostic interventions in female patients.

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Declaration of Competing Interest

The authors have no competing interests to report.

Supplementary data.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jspychores.2021.110589.

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