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Refereed paper

The interpretation of the reasons for encounter 'cough' and 'sadness' in four international family medicine populations

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ABSTRACT

Background This is a study of the relationships between common reasons for encounter (RfEs) and common diagnoses (episode titles) within episodes of care (EoCs) in family practice populations in four countries.

Method Participating family doctors (FDs) recorded details of all their patient contacts in an EoC structure using the International Classification of Primary Care (ICPC), including RfEs presented by the patient, and the FDs' diagnostic labels. The relationships between RfEs and episode titles were studied using Bayesian methods.

Results The RfE 'cough' is a strong, reliable predictor for the diagnoses 'cough' (a symptom diagnosis), 'acute bronchitis', 'URTI' and 'acute laryngitis/tracheitis' and a less strong, but reliable predictor for 'sinusitis', 'pneumonia', 'influenza', 'asthma', 'other viral diseases (NOS)', 'whooping cough', 'chronic bronchitis', 'wheezing' and 'phlegm'. The absence of cough is a weak but reliable predictor to exclude a diagnosis of 'cough', 'acute bronchitis' and 'tracheitis'. Its presence allows strong and reliable exclusion of the diagnoses 'gastroenteritis', 'no disease' and 'health promotion/prevention', and

less strong exclusion of 'adverse effects of medication'. The RfE 'sadness' is a strong, reliable predictor for the diagnoses 'feeling sad/depressed' and 'depressive disorder'. It is a less strong, but reliable predictor of a diagnosis of 'acute stress reaction'. The absence of sadness (as a symptom) is a weak but reliable predictor to exclude the symptom diagnosis 'feeling sad/depressed'. Its presence does not support the exclusion of any diagnosis.

Conclusions We describe clinically and statistically significant diagnostic associations observed between the RfEs 'cough' and 'sadness', presenting as a new problem in family practice, and all the episode titles in ICPC.

Keywords: cough, depressed, diagnosis, electronic medical record, electronic patient record, episode of care, family medicine, general practice, ICPC, International Classification of Primary Care, international, Japan, Malta, posterior probability, prior probability, reason for encounter, sadness, Serbia, symptom, The Netherlands, Transition Project

Introduction

The development of family medicine (FM, synonymous with general practice) as a clinical speciality and an academic discipline is informed and enhanced by the collection of empirical longitudinal data from routine clinical practice. The study of the epidemiology of FM using electronic medical record (EMR) databases represents a classic example, empirically measuring the content of actual practice and informing FM research, education, policy planning and clinical practice.[1,2]

The International Classification of Primary Care (ICPC) acts as an ordering principle for FM data, allowing for direct international comparisons, and has the appropriate granularity for primary care.[3,4] In the Transition Project, such ICPC data have been collected with EMRs in the Netherlands, Japan, Poland, Malta, Serbia and other countries from the daily practice of a cohort of family doctors (FDs) using a similar methodology over time (1 to 11 years). [5–11]

Use of the ICPC to study the epidemiology of FM has the advantage of allowing precise capture of reason for encounter data, often ignored in FM research,[2,11–13] and this allows further important perspectives into the process of diagnosis in FM.

This study aims to support the academic development of FM through the study of the content of episodes of care for two common symptoms in FM, 'cough' and 'sadness' or 'feeling depressed'. The study aims to exemplify how data such as those from the Transition Project may be used to explore the process of diagnosis from a symptom, rather than from a disease, perspective.

The research question for this study is: 'What are the quantitative relationships between common reasons for encounter and common diagnoses (episode titles) within episodes of care in routine family practice in practice populations from Malta, the Netherlands, Serbia and Japan, as exemplified by the reasons for encounter 'cough' and 'sadness/feeling depressed?'

Method

The public-domain EMR TransHis,[10] designed for use with ICPC, was used to collect data from participating FDs who recorded details [reason(s) for encounter, diagnosis(es) and intervention(s)] of all their patient contacts in an episode of care (EoC) structure using ICPC. Reasons for encounter presented by the patient, all FD interventions and the diagnostic labels recorded for each encounter were classified as recommended with ICPC (ICPC-2-E in Malta and Serbia, ICPC-1 in the Netherlands and Japan). All encounter data (face-to-face encounters in the office and at home, telephone consultations, repeat prescriptions, etc.) were analysed in an EoC structure to obtain complete data on incidence and prevalence, including patients presenting for a repeat prescription only.

An EoC is defined as a health problem from its first presentation by the patient to the FD, until the completion of the last encounter for it. It encompasses all contact elements related to that health problem. Its name (i.e. the diagnostic label of the EoC) may be modified over time, and in this article we refer to it as the episode title. The last diagnosis made during an EoC is the current episode title.[4]

The reason(s) for encounter (RfEs) is defined as an agreed statement of the reason(s) why a person enters the healthcare system, representing the demand for care by that person. The RfE should be recognised by the patient as an acceptable description of the demand for care.[4,14,15] FDs recording data for the Transition Project were trained to record RfEs according to the definitions above and the recommendations in the ICPC book,[4] reflecting the patient's symptoms and

requests as expressed. Symptoms elicited during history-taking (i.e. the history of the presenting complaint) were recorded in a separate cell in the EMR TransHis, but were not included in the analyses in this study.

The four databases each encompass a defined period: an average of 9896 patients and 43 577 patient years of observation over five years in Malta (2001–2005), 15 318 patients and 158 370 patient years over 11 years in the Netherlands (1995–2005), 72 673 patient years over one year in Serbia (2003) and 17 042 patient years over three years in Japan (1996–1998). The practice populations in the Netherlands, Serbia and Japan represent registered patient populations (only those over 15 years of age in Serbia), whereas the population in Malta represents patients consulting over a five-year period. The databases were analysed using a one-year data-frame for the purpose of calculating incidence and prevalence rates.

The relationships between RfEs and episode titles were studied using Bayesian probabilistic methods. According to Bayes' Theorem, the post-test (posterior) odds of an event (i.e. a specific diagnosis being made) are equivalent to the pre-test odds multiplied by the likelihood ratio (LR). The LRs presented in the tables were calculated in a method similar to that used by Okkes *et al.*[8,16] The LR was calculated for a problem presenting for the first time at the beginning of a new EoC. We modified the method slightly to calculate LRs for an EoC, rather than for patient years of observation.

The LR is a mathematical expression of the extent to which a symptom increases the probability of a diagnosis. The (positive) LR (LR+) for the existence of the symptom is the odds that it will exist in a patient with the disease, in contrast to a patient without the disease. The (negative) LR (LR–) for absence of the symptom is the odds that the test will be negative in a patient with the disease, contrasted with a patient without the disease. We aggregated or pooled LR values across practices, as we have done in previous studies.[14,15]

It would be possible to analyse such relationships between all possible combinations of episode titles and RfEs, using the Transition Project databases.[8,10] The analysis was limited to two selected RfE examples for practical reasons. The examples chosen were: (1) the most common RfE in all four populations, i.e. 'cough' (ICPC code R05); and (2) an RfE from the mental health ('P') chapter of ICPC which is a common presenting symptom for a number of mental health problems, i.e. the RfE 'sadness' or 'feeling depressed' (ICPC code P03).

In either case, data from each Transition Project population database were analysed step-wise. We first identified episode titles which could potentially have a significant relationship with the index RfE, on the basis that the diagnosis was frequently made in EoCs with that RfE. This was done by analysing the 95% confidence interval (CI) of the rate (expressed as a rate per 1000 observations) of all episode titles presenting for that RfE. If the size of the observation was equivalent to or larger than the width of the 95% CI of that observation itself, the relationship was noted as one which was potentially statistically significant.[1,14,16] All such episode titles were selected for further analysis in all four population databases. The next step was a series of cross-tabulations of both the LR+ and the LR–, performed one-way for the two RfEs against all selected episode titles in each database. If the LRs for all the cross-tabulations above were not clinically and statistically significant (see below) in all four databases, that episode title was excluded from the selection as not being significantly associated with that RfE after all.

The minimum level of clinical significance for an LR was arbitrarily taken as that which represents a standardised difference of at least 0.10 (10%).[1,14–17] Cut-off levels of > 2 for the LR of a positive association and < 0.5 for the LR of a negative association, were thus taken as minimum thresholds for clinical significance.[18–25] LRs outside these limits were considered clinically insignificant. By contrast, LRs outside a second arbitrary threshold (LR+ > 8, LR– < 0.2) were considered to indicate a strong diagnostic association, and indicated as such in our conclusions if present in more than one population. Furthermore, as above, LRs which were not at least as large as their 95% CI were considered unreliable.[1,15–17,26] Furthermore, LRs based on cells with very small numbers were ignored. These criteria adjust for the increased chance of describing spurious associations due to the large numbers of repeated statistical tests in this analysis process, and also for the effect of clustering of data on estimates of variance.[26]

Results

Table 1 gives the incidence and prevalence rates of all selected episode titles with a possible association with the RfE 'cough' (ICPC code R05). The episode title (ICPC code), and incidence and prevalence rates expressed as EoCs per 1000 patient years of observation in the four populations (the Netherlands, Malta, Serbia and Japan) are given. Such data are useful for the calculation of the prior probability of an EoC in the target population.[11,16]

In Table 2, the diagnostic associations are analysed. The LR+ and LR– values for the RfE cough and all the selected episode titles in the four populations are listed. LRs are highlighted according to size (clinical significance) and reliability (95% CI). Strong predictors (LR+ > 8 or LR– < 0.2, CI width smaller than or

Table 1 Incidence and prevalence rates of all selected episode titles with a possible association with the reason for encounter (RfE) 'cough' (ICPC code R05). The episode title, ICPC code, and incidence and prevalence rates expressed as EoCs per thousand patient years of observation in the four populations (the Netherlands, Malta, Serbia and Japan) are given. The code for A92 (Allergy) is not available in ICPC-1 (the Netherlands and Serbia), and the incidence and prevalence rates are thus not applicable (N/A)

Rates per 1000 patient years (Episodes)	The Netherlands		Malta		Serbia		Japan	
	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Cough (R05)	42.3	50.6	23.0	27.6	1.4	2.3	6.7	8.3
Acute bronchitis/bronchiolitis (R78)	41.8	48.6	42.0	43.4	25.5	50.7	17.1	17.8
URTI head cold (R74)	50.5	53.7	202.0	205.7	47.2	99.5	292.3	298.4
Acute laryngitis/tracheitis (R77)	13.9	15.0	16.8	17.8	4.3	7.7	2.0	2.2
Sinusitis (R75)	30.8	35.9	18.3	20.8	5.0	10.9	8.2	9.3
Pneumonia (R81)	9.4	10.7	1.8	2.2	1.5	2.5	5.6	6.9
Influenza (R80)	9.4	9.6	24.8	25.2	1.3	2.2	22.1	22.2
Asthma (R96)	6.7	40.9	12.1	39.3	0.7	4.0	6.6	20.7
Other viral disease NOS (A77)	13.6	14.2	3.0	3.0	0.6	0.9	1.5	1.5
Whooping cough (R71)	1.8	2.0	0.2	0.3	0.2	0.3	0.1	0.1
Acute otitis media/myringitis (H71)	19.8	21.2	11.5	12.1	2.0	3.1	4.6	4.7
Symptoms/complaints throat (R21)	15.8	17.8	2.1	2.2	2.0	3.0	3.5	3.9
Tonsillitis (R76)	14.7	15.5	32.4	34.4	13.8	25.6	11.9	12.3
Adverse effect medication proper dose (A85)	30.7	35.8	14.5	20.8	0.1	0.2	7.7	8.2

Table 1 Continued

Hayfever/allergic rhinitis (R97)	8.8	38.7	10.0	25.4	0.4	0.7	10.6	16.1
Symptoms/complaints chest (L04)	18.5	21.7	3.2	3.6	0.6	1.3	9.4	9.7
Hypertrophy tonsils/adenoids (R90)	3.2	6.6	0.2	0.8	0.2	0.2	0.2	0.2
Shortness of breath/dyspnea (R02)	6.0	7.6	0.5	0.7	0.4	0.6	1.1	1.3
Fever (A03)	6.1	6.4	3.6	3.9	0.6	0.7	7.6	8.1
COPD (R95)	1.5	11.0	0.2	0.9	1.5	6.6	1.2	4.5
General weakness/tiredness (A04)	30.6	37.5	4.2	4.8	0.9	1.5	10.2	11.2
Chronic bronchitis (R91/R79)	0.5	2.4	0.5	1.3	4.7	19.3	0.9	4.2
Other respiratory symptoms/ complaints (R29)	0.6	0.7	23.6	24.4	0.2	0.5	0.2	0.3
Sneezing/nasal congestion (R07)	3.0	4.4	6.0	7.2	0.1	0.1	0.7	0.9
Wheezing (R03)	0.7	0.8	1.4	1.8	0.1	0.3	0.1	0.2

Table 1 Continued

Rates per 1000 patient years (Episodes)	The Netherlands		Malta		Serbia		Japan	
	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Presumed GI infection (D73)	15.3	15.9	79.6	80.6	5.7	10.0	30.8	31.0
Sputum/phlegm abnormal (R25)	0.8	1.0	0.7	0.8	0.0	0.0	1.5	2.2
Strep throat (R72)	2.4	2.5	0.0	0.0	1.9	6.0	1.3	1.5
No disease (A97)	43.2	48.3	42.3	44.3	0.6	0.9	42.8	46.4
Allergy/allergic reaction NOS (A92)	N/A	N/A	4.0	5.4	0.8	1.2	N/A	N/A
Health maintenance/ preventive medicine (A98)	97.9	171.4	90.4	111.6	4.5	5.3	2.3	2.6
Heart failure (K77)	3.5	14.4	2.0	5.1	2.7	14.3	3.6	13.1
Pleurisy/pleural effusion (R82)	0.2	0.3	0.8	0.9	0.2	0.5	0.2	0.3
Muscle pain (L18)	7.3	11.1	40.5	45.0	0.2	0.4	2.3	2.9
Teeth/gum symptom/ complaint (D19)	2.5	2.7	3.6	3.7	0.2	0.3	0.8	0.8

Table 2 Positive (LR+) and negative (LR-) likelihood ratios for the RfE cough for all the selected episode titles (label and ICPC code listed) in the four populations. LRs are highlighted according to size (clinical significance) and reliability (95% CI). Strong predictors (LR+ >8 or LR- <0.2, CI width being equal to or smaller than the size of the observation itself) are in bold type. Weak predictors (LR+ >2–8, LR- 0.2–0.4, small CI) are in italics. Associations with a wide CI (larger than the observation itself) or which are not clinically significant (LR+ <=2, LR- >=0.5) or have a CI which includes unity are not highlighted. The code for A92 (Allergy) is not available in ICPC-1 (the Netherlands and Serbia), and the likelihood ratios are not applicable (N/A)

Rfe (R05) Cough Episode title	The Netherlands		Malta		Serbia		Japan	
	LR+	LR–	LR+	LR–	LR+	LR–	LR+	LR–
Cough (R05)	**20.3 (19.9–20.7)**	*0.2 (0.2–0.2)*	*7.2 (7.1–7.4)*	**0.1 (0.0–0.1)**	12.8 (11.3–14.5)	*0.3 (0.2–0.4)*	**8.1 (7.7–8.6)**	0.1 (0.0–0.1)
Acute bronchitis/ bronchiolitis (R78)	**16.2 (15.8–16.5)**	*0.3 (0.3–0.3)*	*5.6 (5.4–5.8)*	*0.3 (0.3–0.4)*	**11.0 (10.3–11.8)**	0.6 (0.6–0.6)	*5.9 (5.4–6.5)*	*0.4 (0.3–0.4)*
URTI head cold (R74)	**8.5 (8.2–8.7)**	0.6 (0.6–0.6)	*3.2 (3.0–3.3)*	0.7 (0.7–0.8)	**8.3 (7.8–9.0)**	0.7 (0.7–0.7)	**11.8 (10.9–12.8)**	0.6 (0.6–0.6)
Acute laryngitis/ tracheitis (R77)	**12.5 (12.1–12.9)**	*0.4 (0.3–0.4)*	*4.9 (4.6–5.2)*	*0.4 (0.3–0.4)*	**8.9 (7.9–1.0)**	0.5 (0.5–0.6)	1.9 (1.1–3.6)	0.9 (0.7–1.1)
Sinusitis (R75)	*2.8 (2.6–3.0)*	0.9 (0.9–0.9)	1.6 (1.4–1.8)	0.9 (0.9–0.9)	**2.7 (2.1–3.4)**	0.9 (0.9–0.9)	1.3 (0.9–1.9)	1.0 (0.9–1.0)
Pneumonia (R81)	**8.5 (8.0–9.0)**	0.6 (0.5–0.6)	*4.9 (4.3–5.7)*	*0.3 (0.2–0.5)*	*2.7 (1.8–4.2)*	0.9 (0.8–1.0)	*3.3 (2.6–4.2)*	0.7 (0.6–0.8)
Influenza (R80)	*6.3 (5.8–6.7)*	0.7 (0.7–0.7)	*3.1 (2.9–3.3)*	0.7 (0.6–0.7)	*4.7 (3.3–6.5)*	0.8 (0.7–0.9)	*2.3 (1.9–2.7)*	0.8 (0.8–0.9)
Asthma (R96)	*8.0 (7.4–8.5)*	0.6 (0.6–0.6)	*5.5 (5.2–5.7)*	*0.3 (0.2–0.3)*	0.7 (0.2–2.6)	1.0 (1.0–1.1)	*5.2 (4.5–6.0)*	**0.4 (0.3–0.5)**
Other viral disease NOS (A77)	*2.5 (2.2–2.8)*	0.9 (0.9–0.9)	0.1 (0.0–0.4)	1.2 (1.1–1.2)	*4.8 (3.0–7.6)*	0.8 (0.6–0.9)	–	–
Whooping cough (R71)	**14.5 (13.7–15.3)**	*0.2 (0.2–0.3)*	*5.9 (4.6–7.8)*	0.2 (0.0–0.9)	2.6 (0.7–9.3)	0.9 (0.7–1.1)	–	–
Acute otitis media/ myringitis (H71)	0.8 (0.7–1.0)	1.0 (1.0–1.0)	*0.3 (0.2–0.5)*	1.1 (1.1–1.1)	–	–	0.5 (0.2–1.2)	1.1 (1.0–1.1)
Symptoms/ complaints throat (R21)	0.7 (0.5–0.8)	1.0 (1.0–1.0)	0.2(0.0–0.6)	1.2 (1.1–1.2)	0.6 (0.2–1.4)	1.0 (1.0–1.1)	0.4 (0.1–1.2)	1.1 (1.0–1.2)

Table 2 Continued

Rfe (R05) Cough	The Netherlands		Malta		Serbia		Japan	
	LR+	LR–	LR+	LR–	LR+	LR–	LR+	LR–
Tonsillitis (R76)	0.6 (0.5–0.8)	1.0 (1.0–1.0)	0.5 (0.4–0.6)	1.1 (1.1–1.1)	1.0 (0.7–1.2)	1.0 (1.0–1.0)	0.7 (0.5–1.1)	1.0 (1.0–1.1)
Adverse effect medication proper dose (A85)	*0.2 (0.2–0.3)*	1.1 (1.0–1.1)	*0.3 (0.2–0.4)*	1.1 (1.1–1.2)	–	–	1.3 (0.9–1.9)	1.0 (0.9–1.0)
Hayfever/allergic rhinitis (R97)	0.7 (0.6–0.9)	1.0 (1.0–1.0)	1.8 (1.6–2.1)	0.9 (0.8–0.9)	–	–	0.1 (0.0–0.4)	1.1 (1.1–1.1)
Symptoms/ complaints chest (L04)	*0.3 (0.2–0.4)*	1.0 (1.0–1.1)	–	–	–	–	--	–
Hypertrophy tonsils/ adenoids (R90)	1.7 (1.3–2.2)	1.0 (0.9–1.0)	–	–	2.8 (0.8–9.9)	0.9 (0.7–1.1)	–	–
Shortness of breath/ dyspnea (R02)	0.9 (0.6–1.1)	1.0 (1.0–1.0)	0.7 (0.2–2.4)	1.1 (0.9–1.2)	1.1 (0.3–4.3)	1.0 (0.9–1.1)	–	–
Fever (A03)	0.8 (0.6–1.1)	1.0 (1.0–1.0)	0.1 (0.0–0.4)	1.2 (1.1–1.2)	–	–	0.1 (0.0–0.4)	1.1 (1.1–1.2)
COPD (R95)	*3.2 (2.5–4.2)*	0.9 (0.8–0.9)	2.7 (1.3–5.8)	0.7 (0.4–1.2)	1.8 (1.0–3.1)	1.0 (0.9–1.0)	2.1 (1.0–4.4)	0.9 (0.7–1.1)
General weakness/ tiredness (A04)	*0.2 (0.1–0.2)*	1.1 (1.1–1.1)	0.0 (0.0–0.3)	1.2 (1.2–1.2)				
Chronic bronchitis (R79/R91)	**9.8 (8.0–12.1)**	0.5 (0.4–0.6)	*5.6 (4.6–6.8)*	0.2(0.1–0.5)	*2.9 (2.3–3.6)*	0.9(0.8–0.9)	2.7 (1.3–5.6)	0.8 (0.5–1.1)
Other respiratory symptoms/complaints (R29)	0.4 (0.1–1.5)	1.0 (1.0–1.1)	*4.8 (4.5–5.0)*	*0.4 (0.4–0.4)*	–	–	–	–
Sneezing/nasal congestion (R07)	0.5 (0.3–0.9)	1.0 (1.0–1.1)	1.6 (1.3–2.0)	0.9 (0.9–1.0)	–	–	0.7 (0.1–4.5)	1.0 (0.9–1.2)

Table 2 Continued

Wheezing (R03)	*3.3 (2.3–4.9)*	0.9 (0.8–0.9)	*4.2 (3.5–5.1)*	0.5 (0.3–0.6)	–	–	–	–
Presumed GI infection (D73)	**0.1 (0.0–0.1)**	1.1 (1.1–1.1)	**0.1 (0.0–0.1)**	1.2 (1.2–1.2)	–	–	0.1 (0.0–0.2)	1.1 (1.1–1.1)
Sputum/phlegm abnormal (R25)	*2.1 (1.3–3.4)*	0.9 (0.9–1.0)	*4.7 (3.7–5.9)*	*0.4 (0.2–0.6)*	–	–	–	–
Strep throat (R72)	0.6 (0.3–1.0)	1.0 (1.0–1.1)	–	–	*2.9 (2.0–4.2)*	0.9 (0.8–1.0)	0.4 (0.1–2.4)	1.1 (1.0–1.2)
No disease (A97)	**0.1 (0.0–0.1)**	1.1 (1.1–1.1)	**0.1 (0.0–0.1)**	1.2 (1.2–1.2)	0.4 (0.1–2.7)	1.0 (1.0–1.1)	0.0 (0.0–0.1)	1.1 (1.1–1.2)
Allergy/allergic reaction NOS (A92)	N/A	N/A	0.7 (0.4–1.0)	1.1 (1.0–1.1)	–	–	N/A	N/A
Health maintenance/ preventive medicine (A98)	**0.0 (0.0–0.0)**	1.1 (1.1–1.1)	**0.0 (0.0–0.0)**	1.2(1.2–1.2)	–	–	–	–
Heart failure (K77)	0.7 (0.5–1.1)	1.0 (1.0–1.0)	0.6 (0.3–1.2)	1.1 (1.0–1.1)	0.2 (0.0–0.7)	1.1 (1.0–1.1)	0.4 (0.1–1.2)	1.1 (1.0–1.2)
Pleurisy/pleural effusion (R82)	24.7 (2.2–272.3)	1.0 (1.0–1.0)	1.4 (0.8–2.8)	0.9 (0.8–1.1)	1.3 (0.2–8.5)	1.0 (0.8–1.2)	–	–
Muscle pain (L18)	0.1 (0.0–0.2)	1.1 (1.1–1.1)	0.0 (0.0–0.1)	1.2 (1.2–1.2)	–	–	–	–
Teeth/gum symptom/ complaint (D19)	0.0 (0.0–0.3)	1.1 (1.1–1.1)	0.3 (0.1–0.6)	1.1 (1.1–1.2)				

" Black = not significant (LR+ <=2,LR- >=0.5, or wide CI)"
" Italics = weak predictor (LR+ >2–8, LR- 0.2–0.4, small CI)"
" Bold = strong predictor (LR+ >8, LR- <0.2, small CI)"

equal to the LR itself) are in bold type. Weak predictors (LR+ > 2–8, LR– 0.2–0.4, small CI) are in italics. LRs with a wide CI (larger than the observation itself) or which are not clinically significant (LR+ $\leq$ 2, LR– $\geq$ 0.5) or have a CI which includes unity are not highlighted.

The symptom 'cough' is a strong, reliable predictor for the diagnoses 'cough' (a symptom diagnosis), 'acute bronchitis', 'URTI' and 'acute laryngitis/tracheitis' in at least two populations. It is a less strong, but reliable predictor of the diagnoses 'sinusitis', 'pneumonia', 'influenza', 'asthma', 'other viral diseases (NOS)', 'whooping cough', 'chronic bronchitis', 'wheezing' and 'phlegm' with some exceptions, such as the strong association in the Dutch database. The absence of cough (as an RfE) is a less strong but reliable predictor to exclude the diagnoses 'cough', 'acute bronchitis' and 'tracheitis'. Its presence allows strong and reliable exclusion of the diagnoses 'gastroenteritis', 'no disease' and 'health promotion/prevention', and less strong but reliable exclusion of the diagnosis 'adverse effects of medication'. There is less reliable evidence that cough supports making a diagnosis of 'COPD', and supports the exclusion of 'weakness/tiredness' 'muscle pain' and 'teeth/gum complaints' as a diagnosis, since the LRs are clinically significant but outside our CI limits in all but one population.

Table 3 gives the incidence and prevalence rates of all selected episode titles with a possible association with the RfE 'sadness/feeling depressed' (ICPC code P03). The episode title, ICPC code, and incidence and prevalence rates expressed as EoCs per 1000 patient years of observation in the four populations (the Netherlands, Malta, Serbia and Japan) are given. Such data are useful for the calculation of the *prior probability* of an EoC in the target population.[11,16]

In Table 4, the diagnostic associations are analysed. The positive (LR+) and negative (LR–) likelihood ratios for the RfE sadness for all the selected episode titles in the four populations are listed. LRs are highlighted according to size (clinical significance) and reliability (95% CI). Strong predictors (LR+ > 8 or LR– < 0.2, CI width being smaller than or equal to the LR itself) are in bold type. Weak predictors (LR+ > 2–8, LR– 0.2–0.4, small CI) are in italics. LRs with a wide CI (larger than the observation itself) or which are not clinically significant (LR+ $\leq$ 2, LR– $\geq$ 0.5) or have a CI which includes unity are not highlighted.

The symptom 'sadness' is a strong, reliable predictor for the symptom diagnosis 'feeling sad/depressed' and the diagnosis 'depressive disorder' in at least two populations. It is a less strong, but reliable predictor of the diagnosis 'acute stress reaction'. The absence of sadness (as a symptom) is a less strong but reliable predictor to exclude the symptom diagnosis 'feeling sad/depressed'. Its presence does not support the exclusion of any diagnosis in the populations studied. In the Netherlands, 'sadness' is also a strong, reliable predictor for the diagnoses 'anxiety disorder' and 'neurasthenia', and a weak but reliable predictor for the diagnoses 'feeling anxious' and 'relationship problems with partner'. The Maltese LRs, and one Serb LR, are similar, but have wider CIs which do not allow a stronger conclusion on the association.

Discussion

Principal findings

This is a study of the clinical interpretation of two common symptom RfEs, 'cough' and 'sadness', in routine family practice in four practice populations. Data collected with ICPC were used to analyse the diagnostic associations between these two RfEs and diagnoses made during the first encounter of an EoC starting with their presentation to the FD. A number of positive and negative diagnostic associations were found between these two RfEs and a number of episode titles. These associations were found to have different strengths of effect and differing precision of the effect estimate. However, several diagnostic associations were found to be similar in two or more of the databases. A larger database would have given more precise LR estimates, and would likely have demonstrated even more congruence between these diagnostic associations.

Implications of the findings

This study presents diagnostic associations from the perspective of the RfE, making it particularly useful to clinicians dealing with diagnostic challenges in the form of a newly presenting symptom in their daily practice. There were more similarities than differences in the diagnostic associations between RfEs and episode titles across populations, especially evidenced by the more frequent observations with narrower CIs.

Comparisons with the literature

The relative lack of symptoms-oriented research into the diagnostic process in primary care makes finding comparable literature challenging. Most studies of diagnostic associations have been performed in datasets which are not exclusively or mainly from primary care. Additionally, most study a disease label diagnosis and its associations with symptoms and test results as predictors, and not the other way around.[18–25] Even then, the small values proposed for LRs, for example,

Table 3 Incidence and prevalence rates of selected episode titles with a possible association with the RfE 'sadness/feeling depressed' (ICPC code P03). The episode title, ICPC code, and incidence and prevalence rates expressed as EoCs per thousand patient years of observation in the four populations (the Netherlands, Malta, Serbia and Japan) are given

Rates per 1000 patient years (Episodes)	The Netherlands		Malta		Serbia		Japan	
	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Feeling depressed (P03)	5.2	7.4	1.8	2.5	0.4	1.2	0.1	0.2
Depressive disorder (P76)	10.1	36.1	6.7	21.4	2.4	9.7	1.6	5.2
General weakness/tiredness (A04)	30.6	37.5	4.2	4.8	0.9	1.5	10.2	11.2
Acute stress reaction (P02)	5.8	7.9	4.2	5.4	0.7	1.6	0.1	0.1
Feeling anxious/nervous/tense (P01)	12.7	29.8	7.5	12.8	4.4	14.1	1.9	4.4
"Neurasthenia, surmenage (P78)"	4.1	6.1	0.0	0.0	0.2	0.5	0.0	0.0
Anxiety disorder/anxiety state (P74)	2.0	8.8	3.8	14.7	19.1	60.5	1.8	5.2
Relationship problem with partner (Z12)	4.8	6.9	1.4	3.6	0.0	0.0	0.0	0.0

Table 4 Positive (LR+) and negative (LR–) likelihood ratios for the RfE sadness for all the selected episode titles (label and ICPC code listed) in the four populations. LRs are highlighted according to size (clinical significance) and reliability (95% CI). Strong predictors (LR+ >8 or LR– <0.2, CI width being equal to or smaller than the size of the observation itself) are in bold type. Weak predictors (LR+ >2–8, LR– 0.2–0.4, small CI) are in italics. Associations with a wide CI (larger than the observation itself) or which are not clinically significant (LR+ <=2, LR– >=0.5) or have a CI which includes unity are not highlighted

Rfe (P03) Feeling depressed	The Netherlands		Malta		Serbia		Japan	
Episode title	LR+	LR–	LR+	LR–	LR+	LR–	LR+	LR–
Feeling depressed (P03)	**292.8 (269.4–318.2)**	*0.3 (0.3–0.3)*	**146.1 (116.5–183.2)**	*0.4 (0.3–0.5)*	252.8 (92.1–693.8)	0.9 (0.8–1.0)	2279.6 (442.3–11749.4)	0.5 (0.1–2.0)
Depressive disorder (P76)	**108.6 (98.1–120.1)**	0.7 (0.7–0.7)	**188.1(152.7–231.8)**	0.5 (0.5–0.6)	112.8 (49.4–257.9)	1.0 (0.9–1.0)	4216.9 (509.4–34908.4)	0.8 (0.7–1.0)
General weakness/ tiredness (A04)	1.9 (1.4–2.6)	1.0 (1.0–1.0)	2.2 (0.6–8.9)	1.0 (1.0–1.0)	–	–	–	–
Acute stress reaction (P02)	*8.0 (5.6–11.5)*	1.0 (1.0–1.0)	**41.2 (29.3–57.8)**	0.8 (0.8–0.9)	–	–	–	–
Feeling anxious/ nervous/tense (P01)	*3.5 (2.4–5.1)*	1.0 (1.0–1.0)	9.3 (5.5–15.8)	1.0 (0.9–1.0)	–	–	–	–
″Neurasthenia, surmenage (P78)″	**10.4 (7.2–15.2)**	1.0 (1.0–1.0)	–	–	–	–	–	–
Anxiety disorder/anxiety state (P74)	**12.5 (7.8–20.3)**	1.0 (0.9–1.0)	10.1 (5.1–20.2)	1.0 (0.9–1.0)	19.1 (8.6–42.5)	1.0 (1.0–1.0)	–	–
Relationship problem with partner (Z12)	*5.3 (3.3–8.6)*	1.0 (1.0–1.0)	14.2 (5.5–36.8)	1.0 (0.9–1.0)	–	–	–	–

Black = not significant (LR+ <=2,LR- >=0.5, or wide CI)
" Italics = weak predictor (LR+ >2–8, LR- 0.2–0.4, small CI)"
" Bold = strong predictor (LR+ >8, LR- <0.2, small CI)"

for the symptom cough and the diagnoses influenza and community acquired pneumonia[18,20] make one wonder whether they may be generalised to primary care populations. For example, it is difficult to accept the conclusion that no symptom has a clinically significant (defined as an LR of > 2 or < 0.5) predictive value for either influenza or pneumonia in the general population.[18,20] Clinicians routinely diagnose such diseases on the basis of symptoms for which these articles have failed to find a diagnostic association, and many medical textbooks describe relationships between symptoms and such diseases.

In that sense, the diagnostic associations we have found may be more acceptable to and useful for clinicians. Furthermore, the congruency (and often statistical consistency) of diagnostic associations between these populations, and especially the fact that most of them are in the same direction from unity, sustain our confidence in their validity.[14,15] Additionally, the fact that we also present incidence and prevalence rates in these populations allows one to calculate prior and posterior probabilities for these diagnostic entities.

Limitations

This study was based on practice populations, collecting data from actual consultations with the FD. The strength of such empiricism is balanced by the limitation that we did not have data on the actual prevalence and incidence of illness at a community level. We analysed data on EoCs, rather than episodes of illness, in the community.

This study examined associations between RfEs and episode titles at the *beginning* of a new EoC for that problem. It is quite possible that the diagnosis may have been revised over time during another consultation forming part of the EoC due to a change in the presentation, or a change in the diagnostic opinion of the FD, or consequent to the results of further testing, or through an opinion expressed by another healthcare provider, or otherwise. In such cases, the first diagnosis made at the start of the EoC would have been revised at a later consultation within the episode. A different analysis and methodology would be required to capture that transition in the diagnosis, and this is planned for a future study. However, transitions in diagnoses represent a small proportion of EoCs, and in many cases the first diagnosis is the one that persists until the end of the EoC. Nevertheless, the LRs we report should be interpreted with this limitation in mind.

It is possible that the RfEs cough and sadness may have an important effect in increasing the probability of a serious illness to a small but clinically significant degree. In such a case, it is possible that we could miss such an effect due to our strict clinical and statistical limits, and the size limitations of our databases. For example, if the first presentation of the RfE 'cough' slightly increases the probability of a serious and potentially life-threatening disease such as lung cancer, then even such a small effect might have important clinical consequences in a small minority of patients. It is also possible that strong but infrequent associations were not picked up, since we ignored observations based on very small numbers. As such, these data should not be interpreted as supporting the exclusion of serious illness simply on the basis of lack of evidence of diagnostic association with an RfE. The only diagnostic exclusions we would support with these data are those supported by clinically and statistically significant LRs. In any case, the clinical acumen of an experienced FD cannot be entirely summarised by these data, which offer an important insight into clinical decision making, but do not in any way replace it.

A larger dataset would have quite likely picked up more significant associations, and provided more precise estimates of effects. We expect that a larger dataset would have evidenced similar associations between 'sadness' and 'anxiety disorder' and 'relationship problem with partner' in both the Dutch and Maltese datasets, and allowed stronger conclusions to be drawn about both positive and negative diagnostic associations between 'cough' and a number of episode titles in more populations. The observed differences in diagnostic associations between populations may thus be due more to the lack of power to define the LRs more precisely, rather than due to any real difference in diagnostic processing of such RfEs.

The use of the EoC data model allows more precise estimates of incidence and prevalence rates, which is a considerable strength.[3,11] However, many information systems do not allow episode type coding, or do not allow the analysis of diagnostic data structured in EoCs even though the datum may be coded. Thus, replicating this study may be difficult with other datasets.

We have pooled data from different FD practices and across an observation period spanning a number of years. This may open our analyses to criticisms based on the relative size of the interdoctor and interpractice variation compared with variation between populations. We have studied this phenomenon and published our results elsewhere.[15] The effect of interpractice variation is in fact relatively small, and our research leads us to advocate the use of such pooled data. A larger pooled dataset allows much more precise estimations of diagnostic associations as against data from one practice or one year of observation, and the effect of interpractice variation is small enough to be ignored.[15]

There is a challenge in combining information from different populations to produce an 'international'

interpretation of a diagnostic association between a symptom and a diagnosis, or more precisely an RfE and an episode title. We understand the limitations of our interpretation of the diagnostic associations in this study, but we defend our approach. We hereby publish the LRs used to study and describe these diagnostic associations in four different populations, and we offer our interpretation of the strength and reliability of such diagnostic associations, summarising the empirical data in text form. We understand that others may interpret these data differently, or may choose to accept different limits for the clinical and statistical significance of such associations.

Strengths

This is a study of diagnostic associations for two common symptoms in practice populations in very different healthcare settings, which has the advantage of empirical data collection and the validation of observations between four independent datasets. We present these diagnostic data along with associated incidence and prevalence rates which allow one to calculate prior and posterior probabilities for these diagnostic entities in these populations. We collected data on all RfEs presented and all diagnoses made in EoCs, which allows one to study any possible diagnostic association and define those that reach clinical and statistical significance. The presented data are but two examples. We also applied tight clinical and statistical significance limits to avoid describing spurious associations. The congruency of the diagnostic associations across populations sustains our confidence in their validity.

Call for further research

Further research in this area is important to sustain the development of FM as a clinical and academic discipline, and to inform decision-support tools and systems developed for family practice. The assumptions we have made on the clinical and statistical significance limits for a diagnostic association, and the method we have used to interpret and summarise such diagnostic associations in different populations, are presented to the scientific community for discussion.

Conclusions

We describe clinically and statistically significant diagnostic associations observed between the RfEs 'cough' and 'sadness', presenting as a new problem in family practice in four populations, and all the episode titles in ICPC.

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ETHICAL APPROVAL

The study did not involve the collection of new data. Ethical approval was applied for locally, when appropriate, for individual studies based on these data in the Netherlands, Malta, Serbia and Japan.

CONFLICTS OF INTEREST

None.

REFERENCES

1 Okkes IM, Polderman GO, Fryer GE *et al.* The role of family practice in different health care systems. A comparison of reasons for encounter, diagnoses, and interventions in primary care populations in the Netherlands,

Japan, Poland, and the United States. *Journal of Family Practice* 2002;51:72.
2 Hummers-Pradier E *et al. A Research Agenda for Primary Health Care/General Practice in Europe*. European General Practice Research Network: Maastricht, 2009.
3 Soler JK, Okkes I, Lamberts H and Wood M. The coming of age of ICPC: celebrating the 21st birthday of the International Classification of Primary Care. *Family Practice* 2008;25:312–17.
4 Wonca International Classification Committee. *ICPC-2: International Classification of Primary Care* (2e). Oxford University Press: Oxford, 1998.
5 Hofmans-Okkes IM and Lamberts H. The International Classification of Primary Care (ICPC): new applications in research and computer-based primary care information system. *Family Practice* 1996;13:294–302.
6 Kounalakis DK, Lionis C, Okkes I and Lamberts H. Developing an appropriate EPR system for the Greek primary care setting. *Journal of Medical Systems* 2003; 27(3):239–46.
7 Zachariadou T, Floridou D, Angelidou E, Makri L, Philalithis A and Lionis C. Panorama of diagnoses in the primary healthcare setting in Cyprus – data from a pilot study. *European Journal of General Practice* 2004; 10(3):103–4.
8 Okkes IM, Oskam SK, Van Boven K and Lamberts H. EFP. Episodes of Care in Family Practice. Epidemiological data based on the routine use of the International Classification of Primary Care (ICPC) in the Transition Project of the Academic Medical Center/ University of Amsterdam. (1985–2003). In: Okkes IM, Oskam SK and Lamberts H (eds) *ICPC in the Amsterdam Transition Project*. CD-Rom. Academic Medical Center/ University of Amsterdam, Department of Family Medicine: Amsterdam, 2005.
9 Soler JK and Okkes IM. 'Sick leave certification: an unwelcome administrative burden for the family physician?' *European Journal of General Practice* 2004;10(2): 50–5.
10 www.transitieproject.nl (accessed 05/11).
11 Soler JK, Okkes I, Oskam S *et al* for the Transition Project. Is family medicine an international discipline? An international comparative family medicine study of the Transition Project data from the Netherlands, Malta and Serbia. Comparing incidence and prevalence rates of reasons for encounter and diagnostic titles of episodes of care. *Family Practice* 2012. DOI: 10.1093/fampra/ cmr098.
12 Kroenke K and Harris L. Symptoms research: a fertile field. *Annals of Internal Medicine* 2001;134:801–2.
13 Kroenke K. Studying symptoms: sampling and measurement issues. *Annals of Internal Medicine* 2001;134:844–53.
14 Soler JK, Okkes I, Oskam S *et al* for the Transition Project. Is family medicine an international discipline? An international comparative family medicine study of the Transition Project data from the Netherlands, Malta and Serbia. Comparing diagnostic odds ratios. *Family Practice* 2012, DOI: 10.1093/fampra/cmr099.
15 Soler JK, Okkes I, Oskam S *et al* for the Transition Project. An international comparative family medicine study of the Transition Project data from the Netherlands, Malta, Japan and Serbia. Is family medicine an international discipline? Comparing diagnostic odds ratios across age groups, years of observation and individual practices. *Family Practice* 2012, DOI: 10.1093/fampra/ cmr100.
16 Okkes IM, Oskam SK and Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. *Journal of Family Practice* 2002;51(1):31–6.
17 Feinstein AR. Indexes of contrast and quantitative significance for comparisons of two groups. *Statistics in Medicine* 1999;18:2557–81.
18 Metlay JP, Kapoor WN and Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *Journal of the American Medical Association* 1997;278(17):1440–5.
19 Bundy DG, Byerley JS, Liles A, Perrin EM, Katznelson J and Rice HE. Does this child have appendicitis? *Journal of the American Medical Association* 2007;298(4):438–51.
20 Cass SA, Vollenweider MA, Hornung CA, Simel DL and McKinney WP. Does this patient have influenza? *Journal of the American Medical Association* 2005;293(8):987–97.
21 Bent S, Nallamothu BK, Simel DL, Fihn SD and Saint S. Does this woman have an acute uncomplicated urinary tract infection? *Journal of the American Medical Association* 2002;287(20):2701–10.
22 Shaikh N, Morone NE, Lopez J *et al*. Does this child have a urinary tract infection? *Journal of the American Medical Association* 2007;298(24):2895–904.
23 Margaretten ME, Kohlwes J, Moore D and Bent S. Does this adult patient have septic arthritis? *Journal of the American Medical Association* 2007;297(13):1478–88.
24 Trowbridge RL, Rutkowski NK and Shojania KG. Does this patient have acute cholecystitis? *Journal of the American Medical Association* 2003;289(1):80–6.
25 Ebell MH, Smith MA, Barry HC, Ives K and Carey M. The rational clinical examination. Does this patient have strep throat? *Journal of the American Medical Association* 2000;284(22):2912–18.
26 Altman DG, Machin D, Bryant T and Gardner MJ. *Statistics with Confidence. Confidence Intervals and Statistical Guidelines*. BMJ Books: London, 2000.

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