

Impact of COVID-19 on Delays in General Practice. A Retrospective Analysis

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Abstract

Background

From the beginning of the COVID-19 pandemic, worries have been exposed about collateral damage to patients' health through postponed appointments, and delayed diagnostic testing and referrals in general practice.

Aim

To study delays in presentation and management of health problems in general practice during the first 9 months of the COVID-19 crisis. We aimed at symptoms that were most relevant: COVID-19 related symptoms, cancer-related symptoms, mental health symptoms, and musculoskeletal symptoms.

Design and setting

Retrospective analysis of routine patient data from a practice based registration network in the Netherlands (population 40.000 patients; 30 GPs).

Method

We compared data from the first nine months of the COVID-19 crisis to the preceding 5 years, and analyzed differences between the periods of time in the duration of symptoms before presentation, and the duration from the first presentation in general practice until diagnostic testing and referrals.

Results

We found no indications that patients waited longer to contact the FP for newly presented health symptoms; only COVID-19 related symptoms were presented earlier to family practice ($p < 0.001$). Also, we found no delays in general practice for diagnostic testing or referring to hospital care in 2020.

Conclusions

General practice maintained its capability to deliver timely care for newly presented health symptoms during the COVID-19 crisis, despite serious changes in delivery modes: patients have contacted their GPs broadly when it was needed, and do not seem to have postponed their help seeking behavior massively. Follow-up studies are needed to monitor long term consequences also in other health echelons.

Background

In March 2020, the COVID-19 pandemic hit the Netherlands. It had a large and immediate impact on general practice. As was also reported by others,⁽¹⁾ we observed in our practice based network that practices quickly substituted face to face consultations by telephone, video and e-mail consultations. The demand for primary care changed rapidly. More people presented to their GP with other respiratory tract

symptoms, and COVID-19 became the most common respiratory tract related reason for contacting the practice. The number of contacts for other acute and chronic health problems decreased as well as prevention visits, while the number of contacts for mental health visits did not change.(2)

The observed change in presented health problems should trigger concerns of collateral damage to population health due to delay in diagnosis and treatment of important non-COVID-19 conditions. As the pandemic continued, reports have stressed the importance of securing care for all health problems, rather than focusing mainly on COVID-19 care. While reports on postponed primary care for chronic conditions are unambiguous, less is known about newly presented health problems. There are reports of patient delays and fears of visiting a doctor, late diagnostic testing, late referrals, and postponed medical interventions for serious conditions. For example, studies have found an increase of diagnoses for mental health problems,(3) fewer cancer diagnoses,(4, 5) and less fractures.(6) However, it is unclear if accumulation of potentially harmful delays in the process of care happened and in case this occurred whether this was related to the role of primary care. More in particular, it is relevant to comprehend how both patients and GPs reacted to the current COVID-19 crisis. Did patients postpone GP contacts with their GP during the COVID-19 crisis? Did general practitioners respond differently when managing these patients? The answers to these questions may give clues for handling comparable crises in the future, and preparing general medicine for new threats to population's health in the future.

The aim of this study was therefore to establish the changes in newly presented health problems to general practice in the first 9 months of the COVID-19 crisis, differentiating in the periods during and after the first lockdown. More in particular, we explored if patient delays happened in presenting signs and symptoms to general practice by choosing symptoms that are relevant to the COVID-19 crisis clustered in groups: COVID-19 related symptoms, cancer-related symptoms, mental health symptoms, and musculoskeletal symptoms. Furthermore, we studied whether doctor delays occurred in ordering diagnostic tests and referring for these groups of health symptoms.

Methods

Design

Retrospective analysis of routine patient data from a practice based registration network.

Setting

This study was performed in the practice based registration network FaMe-net (Radboud University Medical Center Nijmegen; www.famenet.nl) consisting of 30 general practitioners in the Netherlands, serving a population of approximately 40,000 patients. The population is a bit younger than the Dutch population, but comparable in gender and social class composition.(8) FaMe-net has been recording routine data since 1967. In the Netherlands, patients are listed with a GP, who serves as the first point of access to health care, provides care for the large majority of health problems, and coordinates access to

specialized care.(7) GPs record one or more diagnoses and related interventions for every contact (diagnostic testing, referrals, prescribed medication), under regular review of reliability of coding/classification.(9) FaMe-net classifies each condition in the International Classification of Primary Care (ICPC) and the International Classification of Disease (ICD-10). As a unique feature, FaMe-net registers presented symptoms to general practice as the reason for encounter (RFE), which is the literal utterance of the reason why a person enters the consultation room. These include symptoms, diagnoses and cognitions or fears of illness.(10) Since 2016, as well, the patient's estimation of the duration of symptoms before the first presentation is coded for every new episode of care in hours, days, week or months.

The Radboudumc Technology Center Health Data provides support for extraction and secure storage of routine data from the affiliated practices. It adheres to the regulations of Dutch and European laws and has gained ethical approval from the Radboudumc Medical Ethics Review Committee for this procedure (CMO number 2020-6871). Under Dutch and European privacy laws, it is not necessary to gain informed consent for retrospective studies with anonymised patient data.

Presented symptoms

We selected data from March 16th (the start of the COVID-19 pandemic in the Netherlands) until December 31st 2020, and, in order to contrast the presented symptoms during the pandemic to the preceding years, we also selected data for the years 2016-2019 (March 16th to December 31st). We selected the presented symptoms as a reason to contact the GP for all new episodes of care (ICPC chapter codes 1-99. For further analysis, we selected the four groups of health symptoms as described: COVID-19 related symptoms, cancer-related symptoms, mental health symptoms and musculoskeletal symptoms. We also distinguished between contact modes; practice visits, home visits, telephone consultations as well as e-mail and video-consultations.

For COVID-19 related symptoms, we selected the most commonly presented: cough (R05), dyspnea (R02), thoracic pain (L04, K01, K02, A11), sore throat (R21), fever (A03), common cold (R74), loss of smell/taste (N16), and contacts starting with the question "do I have COVID-19" (R83).

Furthermore, we selected the symptoms that proved to have predictive value for the diagnosis of cancer in general practice:(8) lump in breast (X19), rectal bleeding (D16), postmenopausal bleeding (X12), hematuria (U06), weight loss (T08), hemoptysis (R24), swallowing problems (D21) and change of feces/ bowel habits (D18). For mental health symptoms we distinguished between anxiety/ stress (P01,P02), feeling depressed (P03), sleeping problems (P06), childhood/ adolescent problems (P22, P23), and other mental health symptoms (P04, P05, P07-21). For musculoskeletal symptoms we categorized upper limb symptoms (L08-12), lower limb symptoms (L13-17), back symptoms (L01-L03).

For diagnostic procedures initiated by the general practitioner we used all ICPC codes 33-43, including laboratory testing, pathology, microbiology, endoscopy, radiology, EKG, and the category "other". Referrals

included all referrals to secondary care. We excluded referrals within primary care.

Patient and doctor delay

For each new episode of care, starting with an RFE from the four groups (i.e. COVID-19 related symptoms, alarm symptoms for cancer, mental health symptoms and musculoskeletal symptoms), we extracted the registered duration of symptoms at the first presentation to the practice. This comparison may be considered a proxy for patient delay. Also, we calculated the time from the first presentation to the practice until GPs decided to refer for diagnostic testing or to refer to a medical specialist, also both for 2020 and 2016-2019. This time may be seen as a proxy for potential doctor's delay.

Analysis

The presented health problems were expressed as incidence rates per 1000 patient years. The difference between 2020 and the period 2016-2019 was tested by the incidence rate ratio and 95 % confidence interval. For referrals and diagnostic testing we compared data from 2020 with data from the period 2016-2019. The numbers of diagnostic testing and referrals were related to the number of presented health symptoms to the practice and will be presented as percentages of presented symptoms. The patient's estimation of duration of symptoms at the first visit, was categorized in < 48 hour; 3-7 days; 8-28 days; 29-90 days; and > 90 days. Also the time from the first presentation to diagnostic testing or referral was categorized: same day; 2-7 days; 8-28 days; 29-90 days; > 90 days. A Chi-square test was used to test the difference in distribution over time categories between 2020 and the period 2016-2019. In order to analyze differences in delay during the first lock-down from March 16th until May 15th, compared to the following period until December 31st 2020, we used Chi-square tests for observed differences. A p-value of < 0.05 was considered to be statistically significant, based on two sided tests

Analysis were performed with SPSS version 25 and the fmsb package from R version 3.6.2.(11)

Results

The total number of presented health symptoms to general practice dropped with 15% (2160 vs 2556 per 1000 patient years; $p < 0.001$) in the 9 months following the outbreak of COVID-19 in the Netherlands in March 2020 compared to the years 2016-2019 (2160 vs 2556 per 1000 patient years, respectively; $p < 0.001$). Only respiratory tract symptoms were presented more often in 2020 as compared to the years 2016-2019, although the difference was not significant ($p 0.10$). Symptoms from all other body systems showed a statistically significant drop (Table 1). The number of practice visits and home visits dropped by 37% and 32% respectively (practice visits: 3206 per 1000 patient years (2016-2019) to 2041 per 1000 patient years (2020), home visits 2037 per 1000 patient years (2016-2019) to 138 per 1000 patient years) respectively. Telephone and video consultations and email consultations rose by 85% and 249% resp

(telephone and video 1208 per 1000 patient years (2016-2019) to 2231 per 1000 patient years (2020); email consultations 67 per 1000 patient years (2016-2019) to 234 per 1000 patient years (2020)).

Table 1

Newly presented symptoms to general practice (ICPC chapters; 2020 (n=51,213) compared to 2016-2019 (n=222,634) (n per 1000 patient years))

	ICPC - chapter	2020 n per 1000 patient years	2016-2019 n per 1000 patient years	Difference Rate ratio (95% CI)	Difference p-value
General and non- specified	A	409.0	459.4	0.89 (0.87,0.91)	<0.001
Blood	B	9.7	10.9	0.89 (0.77, 1.03)	0.11
Digestive	D	162.1	201.0	0.81 (0.78, 0.84)	< 0.001
Eye	F	74.3	93.3	0.80 (0.76, 0.84)	< 0.001
Ear	H	102.3	150.3	0.68 (0.65, 0.71)	< 0.001
Circulatory	K	48.1	57.3	0.84 (0.79, 0.89)	< 0.001
Musculoskeletal	L	252.8	326.0	0.78 (0.75, 0.80)	< 0.001
Neurological	N	60.0	72.0	0.84 (0.79, 0.89)	< 0.001
Psychiatry/psychological	P	87.2	101.2	0.86 (0.82, 0.90)	< 0.001
Respiratory	R	247.6	241.7	1.02 (0.99, 1.05)	0.10
Skin	S	359.5	443.7	0.81 (0.79, 0.83)	< 0.001
Endocrine, metabolic	T	24.9	31.2	0.80 (0.73, 0.88)	< 0.001
Urological	U	133.0	144.0	0.92 (0.89, 0.96)	< 0.001
Pregnancy/ child bearing	W	54.0	63.1	0.85 (0.80, 0.91)	< 0.001
Female genital	X	84.6	107.3	0.79 (0.75, 0.83)	< 0.001
Male genital	Y	24.6	26.3	0.94 (0.86, 1.03)	0.16

	ICPC - chapter	2020 n per 1000 patient years	2016-2019 n per 1000 patient years	Difference Rate ratio (95% CI)	Difference p-value
Social problems	Z	26.0	27.6	0.94 (0.86, 1.03)	0.18
Total		2160.2	2556.4	0.85 (0.84, 0.86)	< 0.001

Questions related to COVID-19 became the most common respiratory reason for encounter in 2020. For respiratory symptoms we observed statistical significant differences; cough, fever, fatigue, and sore throat were presented less often than in the years 2016-2019 (p all < 0.001). The frequency of predictive symptoms for the diagnosis of cancer presented in 2020 was comparable to the years 2016-2019, although weight loss and rectal bleeding dropped to some extent. The frequency of mental health symptoms presented dropped, without statistically significant differences for anxiety or depressed feelings. Also, the frequency of musculoskeletal symptoms presented dropped for all grouped symptoms (Table 2).

Table 2

Newly presented symptoms to general practice; COVID-19 related symptoms, cancer-related symptoms, mental health symptoms and musculoskeletal symptoms (2020 compared to 2016-2019 (n per 1000 patient years))

RFE	2020	2016-2019	Difference Rate ratio (95% CI)	Difference p-value
	n per 1000 patient years	n per 1000 patient years		
COVID-19 related symptoms (total)	206.2	223.2	0.89 (0.86,0.91)	<0.001
- Cough	29.1	72.2	0.40 (0.37,0.44)	<0.001
- Thoracic pain	30.2	34.6	1.26 (1.05,1.51)	0.01
- Fever	35.9	48.9	0.74 (0.68,0.79)	<0.001
- Upper respiratory tract infection	16.6	14.8	1.13 (1.01,1.26)	0.04
- Sore throat	21.0	29.9	0.70 (0.64,0.77)	<0.001
- Shortness of breath	22.3	22.3	1.01 (0.91,1.11)	0.90
- Loss smell or taste	0.8	0.5	1.52 (0.89,2.59)	0.1
- COVID-19	50.0	-	-	-
Cancer-related symptoms (total)	22.4	24.0	0.93 (0.85,1.02)	0.14
- Lump breast	6.1	5.3	1.06 (0.88,1.28)	0.53
- Postmenopausal bleeding	1.6	1.1	1.44 (0.99,2.09)	0.06
- Rectal bleeding	4.3	5.6	0.75 (0.61,0.93)	0.01
- Swallowing problems	1.4	1.6	0.95 (0.65,1.39)	0.80
- Change in feces/ bowel habits	3.0	3.3	0.95 (0.73,1.24)	0.71
- Hematuria	3.3	3.1	1.06 (0.83,1.38)	0.61
- Weight loss	2.1	3.0	0.69 (0.51,0.93)	0.02
- hemoptysis	0.6	0.8	0.80 (0.46,1.39)	0.43

RFE	2020	2016-2019	Difference Rate ratio (95% CI)	Difference p-value
Mental Health problems (total)	28.6	31.2	0.92 (0.84,0.99)	0.04
- feeling depressed	5.8	6.6	0.88 (0.73,1.06)	0.18
- anxiety	13.8	13.8	1.00 (0.89,1.13)	0.99
- sleeping problems	7.5	9.2	0.81 (0.69,0.96)	0.01
- child related problems	1.5	1.6	0.92 (0.64,1.33)	0.68
Musculoskeletal symptoms (total)	166.2	216.8	0.77 (0.74,0.79)	<0.001
- vertebral/ neck	35.9	47.1	0.76 (0.71,0.82)	<0.001
- upper limb	58.6	72.1	0.81 (0.77,0.86)	<0.001
- lower limb	71.7	97.6	0.74 (0.70,0.77)	<0.001

For most symptoms the length of time that symptoms existed before patients first contacted their general practitioner did not change in 2020 compared to 2016-2019. Patients reported comparable duration of symptoms for cancer related symptoms, mental health symptoms, and musculoskeletal symptoms. Only for COVID-19 related symptoms more patients contacted their GP statistically significant faster than in 2016-2019 (Table 3). Further analysis of potential delays showed a difference for COVID-19 related symptoms, with a shift to more patients contacting the practice faster after the initial lockdown ended on May 15th ($p < 0.001$). Mental health problems were presented later after the lockdown ended ($p = 0.01$), as well as musculoskeletal symptoms ($p < 0.001$). Symptoms predictive of cancer did not show a difference between 2020 and 2016-2019 ($p = 0.355$).

Table 3

Patient delay. Duration of newly presented symptoms before first presentation to general practice (2020 compared to 2016-2019 (numbers and within group percentages))

RFE	2020		2016-2019		Difference
	n	% (within group)	n	% (within group)	p-value
COVID-related	4,474		20,565		<0.001
- < 48 hour		30.4		18.5	
- 3-7 days		36.6		39.5	
- 1-4 weeks		21.8		29.3	
1-3 months		7.8		9.9	
- > 3 months		3.4		3.0	
Cancer-related symptoms	483		1,861		0.05
- < 48 hour		23.0		24.8	
- 3-7 days		24.2		20.2	
- 1-4 weeks		22.8		21.4	
- 1-3 months		19.0		18.1	
- > 3 months		11.0		15.5	
Mental Health problems	528		2,030		0.21
- < 48 hour		9.5		6.6	
- 3-7 days		5.9		6.6	
- 1-2 weeks		16.7		17.6	
- 1-3 months		33.9		33.5	
- > 3 months		34.1		35.8	
Musculoskeletal symptoms	3,679		16,684		0.04
- < 48 hour		23.1		22.6	
- 3-7 days		22.1		20.0	
- 1-4 weeks		23.6		24.6	
- 1-3 months		19.2		20.5	
- > 3 months		12.0		12.4	

General practitioners ordered additional testing in 2020 for comparable percentages of patients as in preceding years for all groups of symptoms. The time from the first contact with the GP until additional testing was ordered, showed no large differences between symptom groups. Only for COVID-related symptoms additional testing was done significantly later in the trajectory (Table 4).

Table 4

Doctor delay. Duration between the first presentation of newly presented symptoms to general practice until diagnostic testing (2020 compared to 2016-2019; percentage diagnostic testing and within group percentages)

RFE	2020		2016-2019		Difference
	% testing (n)	% within group	% testing (n)	% within group	p-value
COVID-related	12,0 (587/4880)		14,5 (2788/19282)		<0.001
- Same day		52.0		67.3	
- Within 1 week		16.2		13.8	
- Within 1 month		12.9		12.3	
- Within 3 months		13.8		4.9	
- After 3 months		5.1		1.7	
Cancer-related symptoms	45.5 (600/1318)		44.0 (2222/5031)		0,019
- Same day		83.4		86.4	
- Within 1 week		7.8		6.6	
- Within 1 month		5.1		4.8	
- Within 3 months		1.4		1.8	
- After 3 months		2.3		0.4	
Mental Health problems	7.5 (51/681)		9.1 (246/2715)		0,609
- Same day		62.1		70.2	
- Within 1 week		12.6		6.0	
- Within 1 month		9.2		13.1	
- Within 3 months		11.5		7.1	
- After 3 months		4.6		3.6	

RFE	2020		2016-2019		Difference
Muskuloskeletal symptoms	20.7 (819/3954)		21.9 (4134/18836)		0,014
- Same day		74.9		78.1	
- Within 1 week		10.4		7.9	
- Within 1 month		6.8		6.8	
- Within 3 months		5.4		5.2	
- After 3 months		2.5		1.9	

Also, the percentages of patients referred to secondary care were comparable in 2020 as compared to preceding years. The time from the first presentation of symptoms to referral was also similar, but did differ significantly for COVID related symptoms and cancer-related symptoms between 2020 and preceding years, the difference being caused mainly by a difference between referral at the same day and referral within one week. (Table 5).

Table 5

Doctor delay. Duration between the first presentation of newly presented symptoms to general practice until referral to secondary care (2020 compared to 2016-2019; percentage referred and within group percentages)

RFE	2020		2016-2019		Statistics
	% referral (n)	%	% referral (n)	%	
COVID-related	8.0 (389/4880)		8.4 (1620/19282)		0.001
- Same day		53.2		62.9	
- Within 1 week		16.2		15.1	
- Within 1 month		11.6		10.5	
- Within 3 months		11.6		8.0	
- After 3 months		7.5		3.6	
Cancer-related symptoms	18.4 (243/1318)		19.3 (972/5031)		<0.001
- Same day		57.1		68.0	
- Within 1 week		22.3		12.7	
- Within 1 month		12.5		12.0	
- Within 3 months		4.5		6.0	
- After 3 months		3.6		1.3	
Mental Health symptoms	9.4 (64/681)		9.4 (256/2715)		0.086
- Same day		5.1		54.7	
- Within 1 week		9.4		10.9	
- Within 1 month		14.1		12.5	
- Within 3 months		15.6		11.7	
- After 3 months		7.8		10.2	

RFE	2020	2016-2019	Statistics
Musculoskeletal symptoms	9.0 (357/3954)	10.4 (1953/18836)	0.413
- Same day		47.9	48.5
- Within 1 week		13.4	11.5
- Within 1 month		18.8	16.8
- Within 3 months		14.6	15.8
- After 3 months		5.3	7.5

Discussion

In the first 9 months after the start of COVID-19, in the context of large shifts in consultation modes with more emphasis on non-physical contacts, we saw a substantial drop in newly presented health problems to general practice. The presentation of mental health symptoms and cancer-related symptoms dropped, although to a lesser extent than musculoskeletal symptoms and COVID-19 related symptoms. We found no indications that patients waited substantially longer to contact the GP for newly presented health symptoms; only COVID-19 related symptoms were presented earlier to general practice. We also found no indications that GPs themselves delayed diagnostic testing or referrals to hospital care in 2020 for newly presented symptoms.

Our data show that, for newly presented health problems, delays or collateral damage in the delivery of primary care did not occur on a structural basis during the corona crisis. This does not exclude that individual patients may have avoided to contact their general practitioner, or may have postponed their appointments, but it demonstrates that the large majority of patients and general practitioners showed sensible behavior, and did what they would normally do, although sometimes in different care modes. In the past months numerous studies have put emphasis on collateral damage caused by the corona crisis. In a recent Flemish qualitative study general practitioners thought that the corona crisis would have profound impact on the population's psychological and socioeconomic well-being and worried about postponement of appointments.(12) Our study indicates that this seems not the case for the presentation of new episodes of care to general practice in the first year of the COVID-19 crisis. Certainly, the impact of the crisis may still present at a later stage. Another paper from primary care expressed great worries about delayed diagnosis and presentation of cancer related symptoms.(13) Our data do not endorse these worries, although the data shows a slight tendency towards postponement more than three months. Less additional testing and referrals were executed at the same day of presentation, but this was compensated largely within one week of presentation. We presume that this may be related to a change in care modes, for example patients calling or e-mailing the practice, and then being seen in short time in practice. Notably, for the presentation of cancer related symptoms, we did not see a large difference

between the period of the first lockdown shortly after the outbreak, and the following period, although numbers were small.

During the crisis, waiting times in hospitals and overcrowding of intensive care units did lead to serious delays. Our data however suggest that in the Netherlands, with a strong primary care focus, the response to an overwhelming crisis, both from the patients' and from the general practitioners' side, was relatively adequate. Comparable numbers of patients were referred for additional diagnostic procedures and were referred. Delays in presentation of symptoms, additional testing and referrals did not occur in large numbers and did not differ from previous years.

Our study is unique in the way that general practitioners from FaMe-net register data on presenting symptoms and duration of symptoms, as well as interventions and referrals on a daily basis in a very structured way. The practitioners are trained and meet in regular feedback sessions with uniformity testing of coding data in practice. This delivers robust, reliable and high quality data from general practice.⁽⁹⁾ Our study also has limitations. Only data from primary care could be included, meaning that potential delays in hospital settings after referrals were not available for study. Furthermore, we could not analyze precise trends in presentation during the first nine months of the crisis, which, depending on seriousness of lock down measures, may further contribute to insights. The numbers were too small to analyze data on the basis of changes on a weekly basis. We did however, compare data during the first lockdown, with data from the period thereafter, which also gives insight. Our data show insight in four symptom clusters for newly presented symptoms, and thus do not cover the complete spectrum of symptoms presented to general practice. Finally, FaMe-net is a relatively small primary care network in the Netherlands. Conclusions therefore are not generalizable to other health systems and settings, although we do not expect patients in comparable health care systems to behave completely different.

Conclusion

During the corona crisis, Dutch general practice has shown resilience and adaptability to new health care challenges. It has maintained its capability to deliver timely care for newly presented health symptoms, despite serious changes in delivery modes, and more attention to COVID-19 related problems and patients: patients have contacted their general practitioners broadly when it was needed, and do not seem to have postponed their help seeking behavior massively. GPs have been capable of addressing the most urgent care, although this has been at the cost of preventive services and chronic care.⁽²⁾ Follow-up studies are needed to monitor long term consequences of the corona crisis as well.

Declarations

Ethics approval and consent to participate:

- The study protocol was approved by the Research Group of the Department of Primary and Community Care, Radboudumc, Nijmegen, The Netherlands and by the *Radboudumc Medical Ethics*

Review Committee (CMO number 2020-6871).

- The need for informed consent was waived by the *Radboudumc Medical Ethics Review Committee* (also CMO number 2020-6871). The procedure (opt-in/ opt-out) 1/ adheres to the regulations of Dutch and European laws 2/ was approved by the *Radboudumc Medical Ethics Review Committee, Nijmegen, The Netherlands*.
- All research methods are carried out in accordance with Dutch guidelines and regulations. The Radboudumc Technology Center Health Data provided support for extraction and secure storage of routine data from the affiliated practices.

Consent for publication:

- not applicable

Availability of data and materials:

- The datasets generated and analysed during the current study are not publicly available due the fact that the FaMe-Net registration network is the owner of the data, but data are available from the corresponding author on reasonable request.

Competing interests:

- not applicable

Funding:

- not applicable

Authors' contributions:

- HS and KvB conceived the study and wrote the manuscript. EB, ToH, CvW discussed the data and made suggestions to improve the manuscript. RA performed the statistical analysis. All authors read and approved the final manuscript.

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- not applicable

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