ORIGINAL RESEARCH

Health care use before a diagnosis of primary intracranial tumor: a Danish nationwide register study

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Introduction: Detailed knowledge of prediagnostic health care use among patients with primary intracranial tumors is sparse. We aimed to investigate the health care use among adults during the 2 years preceding a diagnosis of a benign or malignant primary intracranial tumor in Denmark.

Methods: We conducted a population-based matched cohort study using historical data from Danish nationwide registries, including all patients aged 30–90 years diagnosed with a first-time primary intracranial tumor from January 1, 2009 to December 31, 2014, and with no prior cancer diagnosis (n=5,926). For each patient, ten comparison subjects were identified using density sampling. We analyzed differences in the frequency and timing of health care use within general practice, physiotherapy, radiology, ear–nose–throat, ophthalmology, neurology, and psychiatry. Odds ratios of having multiple contacts were calculated using a conditional logistical regression model. Monthly incidence rate ratios were estimated using a negative binomial regression model.

Results: Of all patients, 62% had a benign tumor. Patients with benign tumors were more likely to have multiple consultations with health care providers in the period 2–12 months prior to diagnosis and to have increased rates of consultations 1–24 months prior to diagnosis, depending on health service.

Conclusion: Patients diagnosed with a benign or a malignant primary intracranial tumor use the health care services differently. Increased health care use is seen within relatively close proximity to the diagnosis for patients with malignant tumors. However, patients with benign tumors have increased health care use from up to 2 years prior to diagnosis; this suggests a window of opportunity for earlier diagnosis.

Keywords: general practice, diagnosis, brain neoplasms, health care services, Denmark

Introduction

Early diagnosis of primary intracranial tumors is important as some of them, eg, meningiomas, can be radically resected. Additionally, low-grade astrocytomas may transform into high-grade astrocytomas.[1] More than half of the primary intracranial tumors among adults are malignant astrocytoma and meningioma.[2] The prognosis varies from a 5-year survival of glioblastoma of <5% to a 10-year survival of meningioma of 90%.[2]

General practitioners (GPs) are often involved in the diagnosis, particularly in the very early phases of the disease.[3,4] With approximately 1,500 primary intracranial tumor patients annually in Denmark,[5] a Danish GP will on average see 1 patient with an intracranial tumor every third year. Identifying patients in general practice who are suspected of having a primary intracranial tumor is a difficult task as symptoms

of cancer generally have low positive predictive values in general practice.[6]

Primary intracranial tumors often present with specific focal neurological deficits, such as loss of motor function, sensory loss, abnormalities of the visual fields, or with new-onset seizure.[7] Nevertheless, many symptoms of intracranial tumors are vague and nonspecific, such as headache, nausea, dizziness, confusion, anxiety, depression, fatigue, and memory loss; these are symptoms that mostly are caused by other conditions apart from intracranial tumors.[8] All symptoms of brain tumors, except new-onset epilepsy, are individually linked with low risk in general practice.[7] Thus, primary intracranial tumors possess important features seen with prolonged cancer diagnostics in general: low incidence and uncharacteristic symptoms.[9] Delayed diagnosis may have important consequences for the patients in terms of higher mortality and morbidity and more advanced stages of disease at treatment initiation.[10]

Although increased health care use can be a proxy for symptom presentation and how health care professionals act on this symptom presentation,[11] little is known about how and when adults seek health care before a primary intracranial tumor diagnosis. The sparse evidence indicates that a high proportion of patients with a brain tumor has multiple primary care consultations before referral[12] and that children and young patients with central nervous system (CNS) tumors have elevated health care use from 17 months prior to diagnosis.[11]

We aimed to investigate the health care use among adults during the 2 years preceding a diagnosis of a benign or a malignant primary intracranial tumor in Denmark.

Methods

We performed a population-based matched comparative study using national registry data. Data was linked at the individual level by using the Danish civil registration number assigned to all Danish citizens.[13]

Setting

The publicly funded health care system in Demark provides free access for all citizens to general practice and hospital care, and nearly all citizens (98%) are registered with a GP.[14] The GPs are gatekeepers to the rest of the health care system as they carry out initial diagnostic investigations and refer patients to hospitals or outpatient clinics if needed.[15] Patients may, however, contact an ear–nose–throat (ENT) specialist or an ophthalmologist without referral from a GP.[15]

Study population

Patients were identified in the Danish Cancer Registry[16] and were eligible if diagnosed with a first-time primary intracranial tumor, benign (International Classification of Diseases, 10th revision [ICD-10][17]: D320, D330-332, D333B, D333A, D352*, D353, D354) or malignant (ICD-10: C722, C723, C724, C725, C751, C752, C753, C700, C71*), from January 1, 2009 to December 31, 2014, and aged 30–90 years at the date of diagnosis. In total, 6,956 patients were identified.

We excluded 1,030 (14.8%) patients: 822 (11.8%) due to a previous or concurrent cancer (previous nonmelanoma skin cancer [C44] did not result in exclusion), 30 (0.4%) due to no registration at Statistics Denmark, 94 (1.4%) who lived outside Denmark at some point during the 24 months preceding diagnosis, and 84 (1.2%) who were not listed with a general practice.

The study was approved by the Danish Data Protection Agency (file no. 2009-41-3471). According to Danish law, the study did not require approval from the Committee on Health Research Ethics of the Central Denmark Region as no biomedical intervention was performed.

Comparison subjects

Using incidence density sampling, we identified 10 comparison subjects matched on age, gender, and listed general practice for each patient. Information about general practice affiliation was available from the Patient List Register, which holds information on persons assigned to a certain GP at any given time. The index date was defined as the date of the diagnosis of the corresponding patient.

Comparison subjects were not eligible if they fulfilled any of the above listed exclusion criteria for patients. The age difference between patient and the corresponding comparison subject exceeded 2 years for 489 (0.8%) comparison subjects. They were replaced by comparison subjects sampled among patients listed with random general practices in Denmark.

Outcomes

The main outcomes of the study were daytime face-to-face consultations in general practice, including home visits, physiotherapy consultations, radiological examinations, and face-to-face contact with the following specialties: ENT, ophthalmology, neurology, and psychiatry, and all other hospital contacts.

For radiology contacts, we included all types of overall computed tomography, magnetic resonance, X-ray, and ultrasound scans made in primary or secondary care. This approach ensured that all examinations were counted

regardless of the organizational place of the radiological examination, thus making it possible to compare patients with primary intracranial tumors with comparison subjects prior to diagnosis. Data regarding consultations in primary care were extracted from the Danish National Health Service Register,[18] which holds information on all services provided by general practice, physiotherapists, private specialist doctors, and radiological examinations at private radiological clinics for the purpose of remuneration.

Data regarding contacts to somatic hospital (inpatient and outpatient contacts) and data on radiological examinations in secondary health care were extracted from the Danish National Patient Register (DNPR), which contains information on all in- and outpatient contacts at somatic hospitals in Denmark since 1977; outpatient contacts have been included in the register since 1995.[19] Diagnostic information in DNPR is based on the ICD, 8th revision from 1977 to 1993, and the ICD-10 from 1994 to 2016.[19] Information on psychiatric inpatient and outpatient contacts was retrieved from the Danish Psychiatric Central Research Register, which holds information on all patient contacts with psychiatric departments in Denmark.[20]

To investigate the total consultation pattern across medical specialties, the measures of radiological examination, ENT, ophthalmology, neurology, and psychiatry represent the sum of contacts in both primary and secondary health care.

Covariates

The covariates included were age, comorbidity, marital status, income, educational level, labor market affiliation, and country of origin. Additionally, information on known diseases within 4 medical specialties of interest (ENT, ophthalmology, neurology, and psychiatry) was used for subanalyses.

Age was defined as the age at the index date. To adjust for comorbidity, the Charlson Comorbidity Index (CCI) was calculated[21] based on diagnoses registered in the DNPR 10 years prior to the study entry (2 years prior to the index date) and grouped into "None" (CCI score =0), "Moderate" (CCI score =1–2), and "Severe" (CCI score ≥3).

Demographic and socioeconomic information was collected from Statistics Denmark.[22] Marital status was categorized into "Living alone" or "Married/Cohabitating." Data on taxable income was extracted for the calendar year preceding the index date to eliminate the risk of influence from the primary intracranial tumor diagnosis. Income was subdivided into 3 equally sized groups using the OECD-modified scale and classified as "Low," "Middle", or "High" income.[23] The highest attained level of education was categorized into "Basic," "Short", and "Long" according to the International Standard Classification of Education.[24] Labor market affiliation based on the main employment during the preceding 12 months was categorized into "Working," "Unemployed" (including maternity leave and unspecified leave), and "Retired" (including persons on early retirement and persons receiving early retirement benefit). Country of origin was categorized as "Danish" or "Immigrant."

Persons with missing information on marital status (n=1) were categorized as "Cohabiting." Persons with missing information on income (n=1) were categorized as "Low income." Persons with missing information on education (357 patients, 3,854 comparison subjects) were categorized as "Basic education," as these persons are most often uneducated.[25] Persons with missing information on labor market affiliation (200 patients, 2,009 comparison subjects) were categorized as "Unemployed," as these persons most often have no income,[26] and persons with missing information on nationality (n=1) were categorized as "Danish."

Data on known diseases within the 4 specific medical specialties ENT, ophthalmology, neurology, and psychiatry, were retrieved from the DNPR according to medical specialty-specific ICD-10 codes, except for diagnoses already accounted for in the CCI. The known diseases of interest were defined as ENT: "diseases in ear and mastoid process of temporal bone (DH60-DH95);" ophthalmology: "diseases in eye and orbital region (DH00-DH59);" neurology: "diseases in the nervous system (G00-G29, G31-G44, G46-G79, and G83-G99);" and psychiatry: "psychiatric disease and behavioral disorders (F03-F05.0 and F05.2-F99)."

Statistical analysis

Analyses were stratified on whether patients were diagnosed with a benign or a malignant primary intracranial tumor. The analyses were performed for each sex separately because of known gender differences in the health care utilization.[27]

Odds ratios (ORs) of having consultations in the year prior to diagnosis (omitting the last month before diagnosis) were estimated using conditional logistical regression to account for the matched design.

A negative binominal regression model applying cluster robust variance at the patient level was used to estimate incidence rate ratios (IRRs) for comparison of the monthly rates of health care contacts between patients and comparison subjects in the entire 2-year period before diagnosis.

Analyses were adjusted for age, comorbidity, marital status, income, educational level, labor market affiliation, and country of origin.

To investigate if known diseases within a medical specialty influenced the estimates, we undertook subanalyses on the ORs of having a consultation at ENT, ophthalmology, neurology, and psychiatry, by adjusting for the presence of known disease of the specific medical specialty in question (ie, the ORs of having a consultation in ophthalmology was also adjusted for known diseases in the eye and orbital region).

Data were analyzed using the statistical software Stata 14 (StataCorp LP, College Station, TX, USA).

Results

The study included 5,926 incident first-time primary intracranial tumor patients and 59,260 comparison subjects. Of the patients identified 3,654 (62%) had a benign tumor (70% among women and 52% among men, respectively).

The patients and the comparison subjects were generally comparable, although more patients with benign tumors than their comparison subjects had comorbidity (Table 1). The opposite trend was observed for patients with malignant tumors.

Patients with benign primary intracranial tumors

In the year preceding diagnosis (omitting the last month before diagnosis), the proportion of female patients diagnosed with a benign tumor who consulted the different health care providers were as follows: GP: 91.1%, physiotherapy: 14.1%, radiology: 47.2%, ENT: 19.2%, ophthalmology: 24.0%, neurology: 7.4%, psychiatry: 3.6%, and other hospital contacts: 45.6% (Table 2). The numbers were slightly lower for men.

Table 1 Characteristics of the study population of patients with benign or malignant primary intracranial tumors diagnosed in 2009–2014 stratified on gender

Benign tumors

	Women						Men					
	Comparison subjects		Patients		Total		Comparison subjects		Patients		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
	22,160	90.9	2,216	9.1	24,376	100	14,380	90.9	1,438	9.1	15,818	100
Age group (years)												
30–49	6,090	27.5	609	27.5	6,699	27.5	3,920	27.3	392	27.3	4,312	27.3
50–69	10,350	46.7	1,035	46.7	11,385	46.7	7,210	50.1	721	50.1	7,931	50.1
70–90	5,720	25.8	572	25.8	6,292	25.8	3,250	22.6	325	22.6	3,575	22.6
Country of origin												
Danish	20,445	92.3	2,058	92.9	22,503	92.3	13,313	92.6	1,342	93.3	14,655	92.6
Immigrant	1,715	7.7	158	7.1	1,873	7.7	1,067	7.4	96	6.7	1,163	7.4
Marital status												
Cohabiting	13,915	62.8	1,390	62.7	15,305	62.8	10,384	72.2	1,054	73.3	11,438	72.3
Living alone	8,245	37.2	826	37.3	9,071	37.2	3,996	27.8	384	26.7	4,380	27.7
Educational level												
Basic	7,907	35.7	779	35.2	8,686	35.6	4,255	29.6	428	29.8	4,683	29.6
Short	8,069	36.4	814	36.7	8,883	36.4	6,543	45.5	633	44.0	7,176	45.4
Long	6,184	27.9	623	28.1	6,807	27.9	3,582	24.9	377	26.2	3,959	25.0
Labor market affiliation												
Working	10,453	47.2	992	44.8	11,445	47.0	7,718	53.7	756	52.6	8,474	53.6
Unemployed	1,384	6.2	153	6.9	1,537	6.3	757	5.3	84	5.8	841	5.3
Retirement pension	10,323	46.6	1,071	48.3	11,394	46.7	5,905	41.1	598	41.6	6,503	41.1
Income												
Low	7,477	33.7	759	34.3	8,236	33.8	4,132	28.7	416	28.9	4,548	28.8
Middle	7,476	33.7	736	33.2	8,212	33.7	4,855	33.8	481	33.4	5,336	33.7
High	7,207	32.5	721	32.5	7,928	32.5	5,393	37.5	541	37.6	5,934	37.5
Comorbidity												
Low	18,385	83.0	1,786	80.6	20,171	82.7	11,715	81.5	1,145	79.6	12,860	81.3
Moderate	2,486	11.2	274	12.4	2,760	11.3	1,625	11.3	179	12.4	1,804	11.4
Severe	1,289	5.8	156	7.0	1,445	5.9	1,040	7.2	114	7.9	1,154	7.3

(*Continued*)

Table 1 (*Continued*)

Malignant tumors

	Women						Men					
	Comparison subjects		Patients		Total		Comparison subjects		Patients		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
	9,510	90.9	951	9.1	10,461	100	13,210	90.9	1,321	9.1	14,531	100
Age group (years)												
30–49	1,320	13.9	132	13.9	1,452	13.9	2,140	16.2	214	16.2	2,354	16.2
50–69	4,690	49.3	469	49.3	5,159	49.3	7,170	54.3	717	54.3	7,887	54.3
70–90	3,500	36.8	350	36.8	3,850	36.8	3,900	29.5	390	29.5	4,290	29.5
Country of origin												
Danish	8,939	94.0	900	94.6	9,839	94.1	12,379	93.7	1,252	94.8	13,631	93.8
Immigrant	571	6.0	51	5.4	622	5.9	831	6.3	69	5.2	900	6.2
Marital status												
Cohabiting	5,667	59.6	577	60.7	6,244	59.7	9,554	72.3	967	73.2	10,521	72.4
Living alone	3,843	40.4	374	39.3	4,217	40.3	3,656	27.7	354	26.8	4,010	27.6
Educational level												
Basic	3,940	41.4	420	44.2	4,360	41.7	4,255	32.2	424	32.1	4,679	32.2
Short	3,299	34.7	325	34.2	3,624	34.6	6,026	45.6	585	44.3	6,611	45.5
Long	2,271	23.9	206	21.7	2,477	23.7	2,929	22.2	312	23.6	3,241	22.3
Labor market affiliation												
Working	3,341	35.1	328	34.5	3,669	35.1	6,223	47.1	641	48.5	6,864	47.2
Unemployed	419	4.4	42	4.4	461	4.4	589	4.5	50	3.8	639	4.4
Retirement pension	5,750	60.5	581	61.1	6,331	60.5	6,398	48.4	630	47.7	7,028	48.4
Income												
Low	3,646	38.3	366	38.5	4,012	38.4	4,191	31.7	374	28.3	4,565	31.4
Middle	3,095	32.5	317	33.3	3,412	32.6	4,394	33.3	462	35.0	4,856	33.4
High	2,769	29.1	268	28.2	3,037	29.0	4,625	35.0	485	36.7	5,110	35.2
Comorbidity												
Low	7,594	79.9	779	81.9	8,373	80.0	10,306	78.0	1,070	81.0	11,376	78.3
Moderate	1,215	12.8	116	12.2	1,331	12.7	1,724	13.1	158	12.0	1,882	13.0
Severe	701	7.4	56	5.9	757	7.2	1,180	8.9	93	7.0	1,273	8.8

Patients with benign tumors had higher odds of having 5–9 consultations in general practice than comparison subjects (both sexes), and female patients had higher odds of having ≥10 consultations in general practice than the comparison subjects (Table 2).

Overall, female and male patients had higher likelihood of having 1 or more contacts to ophthalmology, ENT, and neurology than the comparison subjects (Table 2). Female patients had a particularly higher likelihood of ≥3 neurology contacts than the comparison subjects, which was not seen for male patients. Additionally, both male and female patients had higher odds of having 1 or more radiology contacts than the comparison subjects.

Overall, patients with benign tumors had significantly more consultations than the comparison subjects 1–24 months prior to diagnosis peeking the last month prior to diagnosis (Figures 1, 3, and S1). The starting point of increased health care use differed between male and female

patients, eg, for general practice (men: 11 months, women: 20 months) and neurology (men: 9 months, women: 21 months). Further, the starting point of increased health care use differed across specialties, eg, ENT (both men and women: 24 months).

The peak in consultations 2 months prior to diagnosis ranged from 36% more consultations for physiotherapy (IRR_{women}=1.36 [95% confidence interval [CI]: 1.08; 1.72]) to 19 times more consultations within neurology (IRR_{women}=9.61 [95% CI: 15.83; 24.29]) (Figures 1 and 3).

Patients with malignant primary intracranial tumors

In the year preceding diagnosis (omitting the last month before diagnosis), the proportion of female patients diagnosed with a malignant tumor who consulted the different health care providers were as follows: GP: 87.1%, physiotherapy: 13.5%, radiology: 39.0%, ENT: 14.2%,

Table 2 The associations (OR) between health care contacts and being diagnosed with a benign or malignant primary intracranial tumor (patients) or not (comparison subjects)

Benign tumors

Number of contacts by specialty	Women						Men					
	Patients		Comparison subjects		OR	95% CI	Patients		Comparison subjects		OR	95% CI
	n	%	n	%			n	%	n	%		
GP												
0	198	8.9	2,959	13.4	0.65	0.56–0.76	239	16.6	3,411	23.7	0.64	0.55–0.74
1–4	938	42.3	10,292	46.4	0.86	0.78–0.94	704	49.0	6,840	47.6	1.07	0.95–1.19
5–9	691	31.2	5,858	26.4	1.25	1.14–1.38	334	23.2	2,721	18.9	1.30	1.14–1.49
≥10	389	17.6	3,051	13.8	1.35	1.20–1.53	161	11.2	1,408	9.8	1.14	0.94–1.37
Physiotherapy (primary care)												
0	1,903	85.9	19,467	87.8	0.84	0.74–0.96	1,308	91.0	13,371	93.0	0.76	0.63–0.92
1–3	60	2.7	681	3.1	0.89	0.68–1.16	38	2.6	323	2.2	1.17	0.83–1.65
≥4	253	11.4	2,012	9.1	1.28	1.12–1.47	92	6.4	686	4.8	1.37	1.09–1.72
Radiology contacts												
0	1,169	52.8	13,414	60.5	0.70	0.64–0.77	948	65.9	10,940	76.1	0.60	0.53–0.67
1	445	20.1	3,724	16.8	1.27	1.13–1.44	198	13.8	1,502	10.4	1.36	1.15–1.60
2	204	9.2	1,834	8.3	1.11	0.95–1.29	123	8.6	760	5.3	1.68	1.37–2.05
≥3	398	18.0	3,188	14.4	1.29	1.14–1.45	169	11.8	1,178	8.2	1.51	1.26–1.80
ENT												
0	1,791	80.8	19,677	88.8	0.52	0.47–0.59	1,157	80.5	12,826	89.2	0.49	0.42–0.57
1–2	279	12.6	1,816	8.2	1.63	1.42–1.87	177	12.3	1,120	7.8	1.67	1.41–1.98
≥3	146	6.6	667	3.0	2.28	1.89–2.76	104	7.2	434	3.0	2.52	2.01–3.16
Ophthalmology												
0	1,684	76.0	17,717	80	0.79	0.71–0.88	1,153	80.2	12,210	84.9	0.69	0.60–0.81
1–2	368	16.6	3,256	14.7	1.15	1.01–1.30	215	15.0	1,593	11.1	1.45	1.23–1.70
≥3	164	7.4	1,187	5.4	1.42	1.19–1.70	70	4.9	577	4.0	1.21	0.93–1.58
Neurology												
0	2,053	92.6	21,299	96.1	0.53	0.45–0.64	1,359	94.5	13,842	96.3	0.68	0.53–0.87
1–2	102	4.6	652	2.9	1.53	1.22–1.90	59	4.1	395	2.7	1.47	1.11–1.96
≥3	61	2.8	209	0.9	2.74	2.01–3.74	20	1.4	143	1.0	1.51	0.94–2.43
Psychiatry												
0	2,137	96.4	21,444	96.8	1.00	0.78–1.29	1,394	96.9	14,056	97.7	0.71	0.48–1.03
1–2	19	0.9	216	1.0	0.74	0.44–1.22	19	1.3	100	0.7	1.91	1.07–3.39
≥3	60	2.7	500	2.3	1.12	0.83–1.51	25	1.7	224	1.6	1.20	0.74–1.93
Other hospital specialties												
0	1,205	54.4	13,985	63.1	0.70	0.64–0.77	837	58.2	9,697	67.4	0.67	0.59–0.75
1–2	499	22.5	4,054	18.3	1.29	1.16–1.44	300	20.9	2,580	17.9	1.20	1.04–1.37
≥3	512	23.1	4,121	18.6	1.29	1.16–1.44	301	20.9	2,103	14.6	1.57	1.37–1.81

Malignant tumors

Number of contacts by specialty	Women						Men					
	Patients		Comparison subjects		OR	95% CI	Patients		Comparison subjects		OR	95% CI
	n	%	n	%			n	%	n	%		
GP												
0	123	12.9	1,222	12.8	1.00	0.81–1.23	293	22.2	2,836	21.5	1.03	0.89–1.19
1–4	427	44.9	4,241	44.6	1.01	0.88–1.16	607	46.0	6,022	45.6	0.99	0.88–1.12
5–9	271	28.5	2,619	27.5	1.05	0.91–1.22	295	22.3	2,819	21.3	1.09	0.95–1.26
≥10	130	13.7	1,428	15.0	0.90	0.74–1.11	126	9.5	1,533	11.6	0.85	0.70–1.05
Physiotherapy (primary care)												
0	823	86.5	8,346	87.8	0.88	0.72–1.08	1,226	92.8	12,295	93.1	0.98	0.79–1.22
1–3	28	2.9	257	2.7	1.12	0.75–1.68	31	2.3	267	2.0	1.13	0.77–1.66
≥4	100	10.5	907	9.5	1.13	0.90–1.41	64	4.8	648	4.9	0.97	0.75–1.26

(Continued)

Table 2 (*Continued*)

Malignant tumors

Number of contacts by specialty	Women						Men					
	Patients		Comparison subjects		OR	95% CI	Patients		Comparison subjects		OR	95% CI
	n	%	n	%			n	%	n	%		
Radiology contacts												
0	580	61.0	5,794	60.9	0.99	0.85–1.14	973	73.7	9,756	73.9	0.95	0.83–1.09
1	155	16.3	1,550	16.3	1.01	0.83–1.22	157	11.9	1,469	11.1	1.08	0.91–1.29
2	73	7.7	857	9.0	0.84	0.65–1.08	74	5.6	749	5.7	1.00	0.78–1.29
≥3	143	15.0	1,309	13.8	1.15	0.95–1.40	117	8.9	1,236	9.4	1.01	0.82–1.25
ENT												
0	816	85.8	8,315	87.4	0.87	0.71–1.06	1,169	88.5	11,641	88.1	1.04	0.87–1.24
1–2	99	10.4	902	9.5	1.11	0.89–1.39	103	7.8	1,121	8.5	0.91	0.73–1.12
≥3	36	3.8	293	3.1	1.25	0.87–1.79	49	3.7	448	3.4	1.12	0.82–1.52
Ophthalmology												
0	727	76.4	7,357	77.4	0.94	0.80–1.11	1,099	83.2	10,924	82.7	1.01	0.86–1.18
1–2	159	16.7	1,547	16.3	1.04	0.87–1.25	149	11.3	1,682	12.7	0.90	0.75–1.08
≥3	65	6.8	606	6.4	1.09	0.83–1.43	73	5.5	604	4.6	1.23	0.95–1.59
Neurology												
0	903	95.0	9,123	95.9	0.81	0.60–1.10	1,253	94.9	12,695	96.1	0.72	0.55–0.94
1–2	30	3.2	296	3.1	0.96	0.66–1.39	54	4.1	377	2.9	1.51	1.12–-2.03
≥3	18	1.9	91	1.0	2.00	1.19–3.34	14	1.1	138	1.0	1.08	0.62–1.89
Psychiatry												
0	922	97.0	9,225	97	0.94	0.63–1.40	1,297	98.2	12,936	97.9	1.03	0.66–1.59
1–2	7	0.7	94	1.0	0.71	0.31–1.61	<5	–	96	0.7	0.49	0.18–1.28
≥3	22	2.3	191	2.0	1.25	0.80–1.95	20	1.5	178	1.3	1.24	0.75–2.04
Other hospital specialties												
0	621	65.3	5,959	62.7	1.09	0.94–1.27	881	66.7	8,673	65.7	1.00	0.88–1.13
1–2	164	17.2	1,755	18.5	0.93	0.78–1.11	227	17.2	2,308	17.5	0.99	0.85–1.15
≥3	166	17.5	1,796	18.9	0.95	0.79–1.14	213	16.1	2,229	16.9	1.03	0.87–1.21

Notes: Adjusted for country of origin, CCI, marital status, income, labor market affiliation, highest educational level.
Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ENT, ear–nose–throat; GP, general practitioner; OR, odds ratio.

ophthalmology: 23.6%, neurology: 5.0%, psychiatry: 3.0%, and other hospital contacts: 34.7% (Table 2). The numbers were slightly different for men.

The patients did not show higher likelihood of having consulted any of the health care professionals during the period 2–12 months prior to diagnosis than the comparison subjects, except for neurology consultations. Male patients had higher odds of having 1 or 2 consultations with a neurologist, and female patients had higher odds of having 3 or more consultations with a neurologist relative to their comparison subjects (Table 2).

In general, patients with malignant tumors had significantly more consultations than the comparison subjects 1–7 months prior to diagnosis, peaking in the last month prior to diagnosis (Figures 2, 4, and S2). The starting point of increased health care use differed between male and female patients, eg, general practice (women: 4 months, men: 6 months) and neurology (women: 7 months, men: 5 months) and across medical specialties (Figures 2, 4, and S2).

The peak in consultations 2 months prior to diagnosis ranged from 61% more consultations with a GP (IRR_{women}=1.61 [95% CI: 1.45; 1.79]) to more than 16 times more neurology consultations (IRR_{women}=16.74 [95% CI: 11.32; 24.75]) (Figures 2 and 4).

Subanalyses
Overall, similar results were seen when adjusting for known specialty-specific disease (Table S1), although the ORs of having 1–2 ophthalmology consultations for women with benign tumors and of having 1–2 neurology consultations for men with benign tumors were no longer significant.

Discussion
Main findings
This study on data from almost 6,000 patients diagnosed with a primary intracranial tumor shows that patients diagnosed with benign and malignant primary intracranial tumors use health care differently in the time prior to diagnosis. Patients
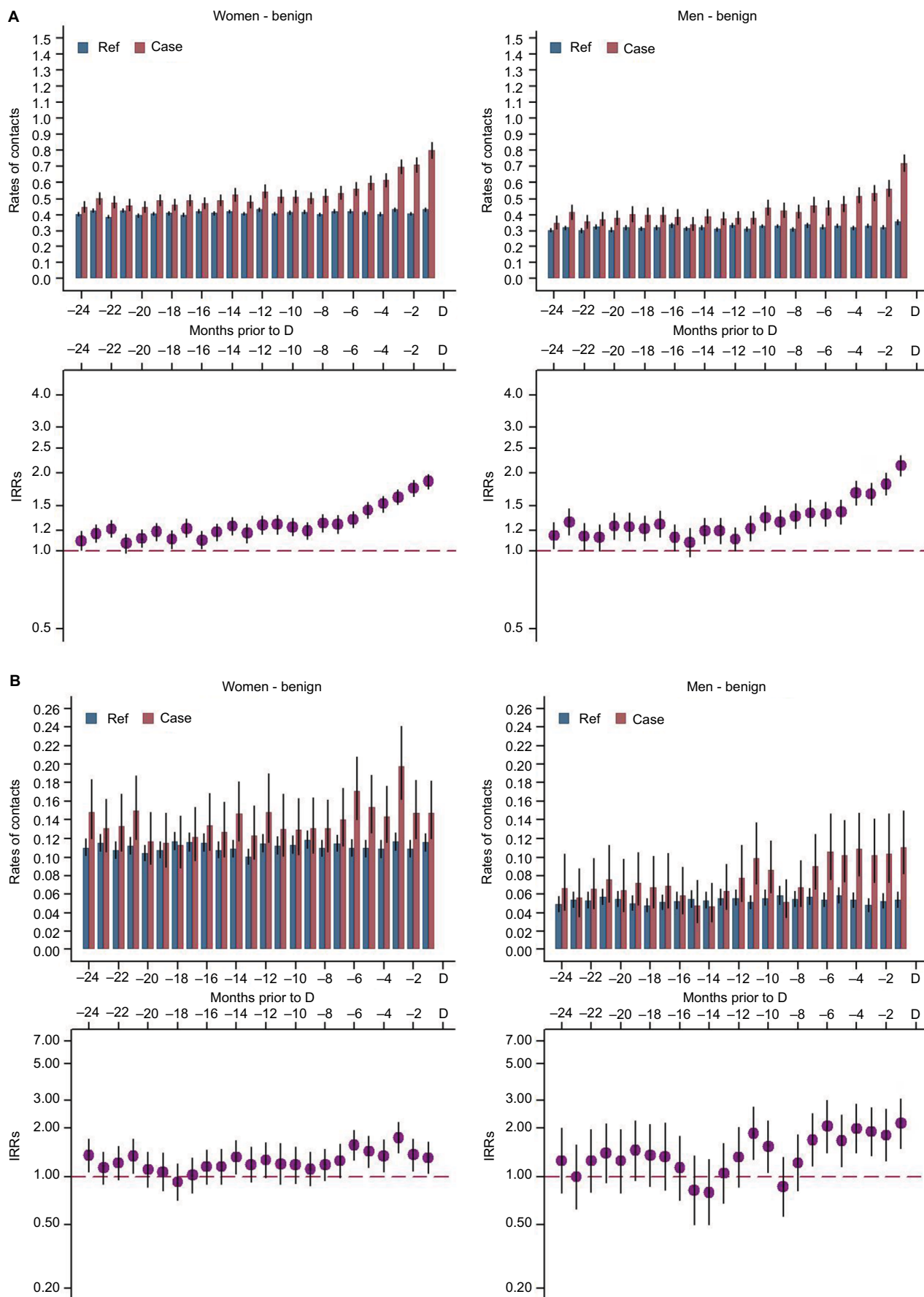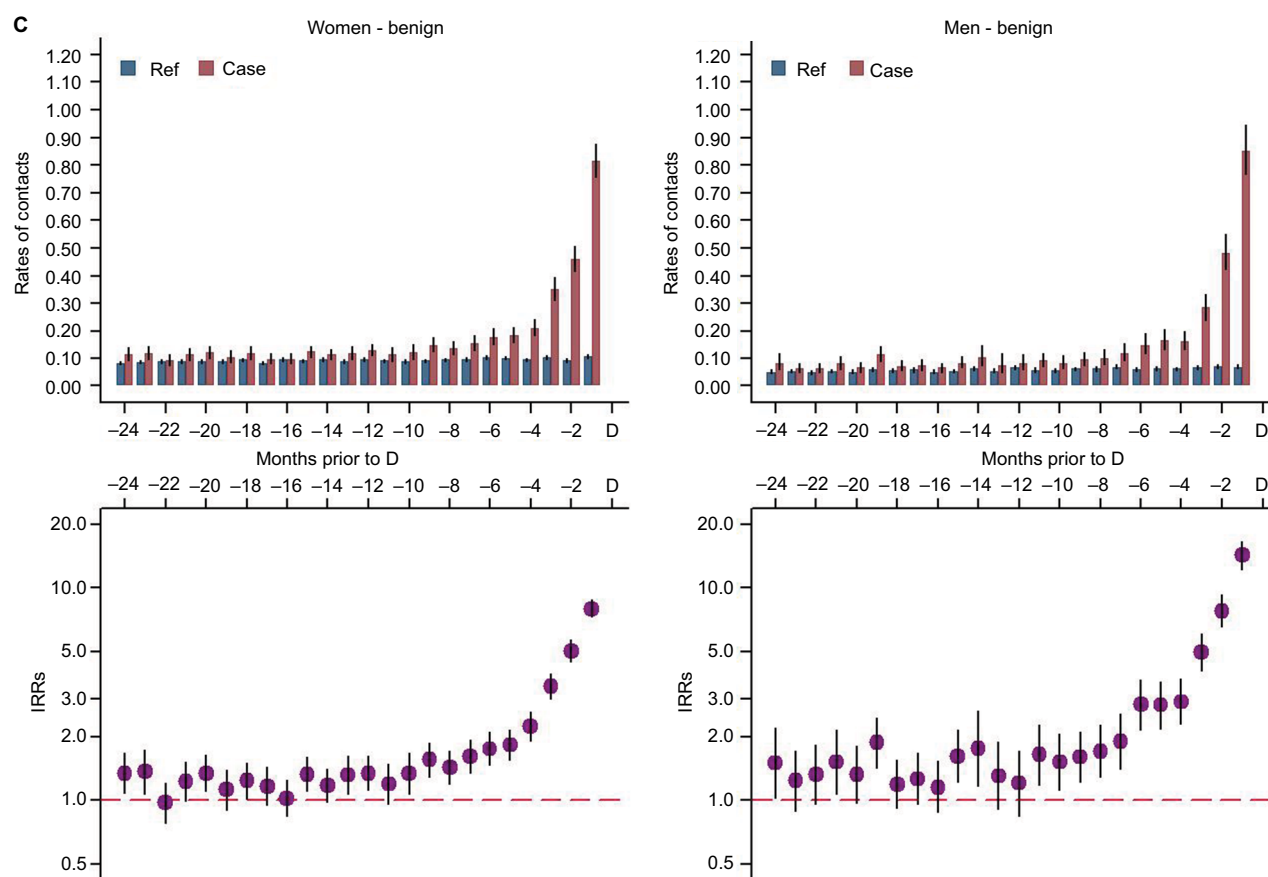
Figure I (*Continued*)

Figure 1 Total health care contacts to GP (daytime) (**A**) physiotherapy (**B**), and radiological examinations (**C**) among patients with benign primary intracranial tumors.
Notes: Upper parts of **A–C**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A–C**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; GP, general practitioner; IRR, incidence rate ratio; Ref, reference.

with malignant tumors had increased health care use in relatively close proximity to the diagnosis, whereas patients with benign tumors had increased health care use for a long time before diagnosis. Most notably, patients with benign tumors had increased health care use 24 months prior to diagnosis for ENT consultations, from 21 months prior to diagnosis for neurology consultations, and from 12 months prior to diagnosis for ophthalmology consultations.

Strengths and limitations

The strengths of this study include the population-based design, which was permitted by the uniformly organized health care system in Denmark, the use of the data from the complete Danish registries,[18,19,28] and the identification of patients in the Danish Cancer Registry.[16] The comparison subjects were randomly sampled by a density sampling procedure and thus should be representative of the source population concerning health care use.

Although we used the Danish Cancer Registry to identify patients, misclassification of tumors as either malignant or benign may still occur as the diagnosis may have been based solely on neuroimaging.[29,30] However, such misclassification should result in an underestimation of the associations found. Some information on educational level and labor market affiliation was missing. The missing data was distributed equally between patients and comparison subjects, and inclusion of these data should not bias the results.

We minimized the risk of confounding by matching comparison subjects and patients according to gender, age, and general practice and by adjusting the analyses for socioeconomic and demographic factors. However, residual confounding may still prevail. Yet, the risk of residual confounding should be equally distributed for both patients and comparison subjects, which is likely to lead to an underestimation of the associations.

We restricted the primary intracranial tumor population to first-time cancers only to avoid the influence of potentially
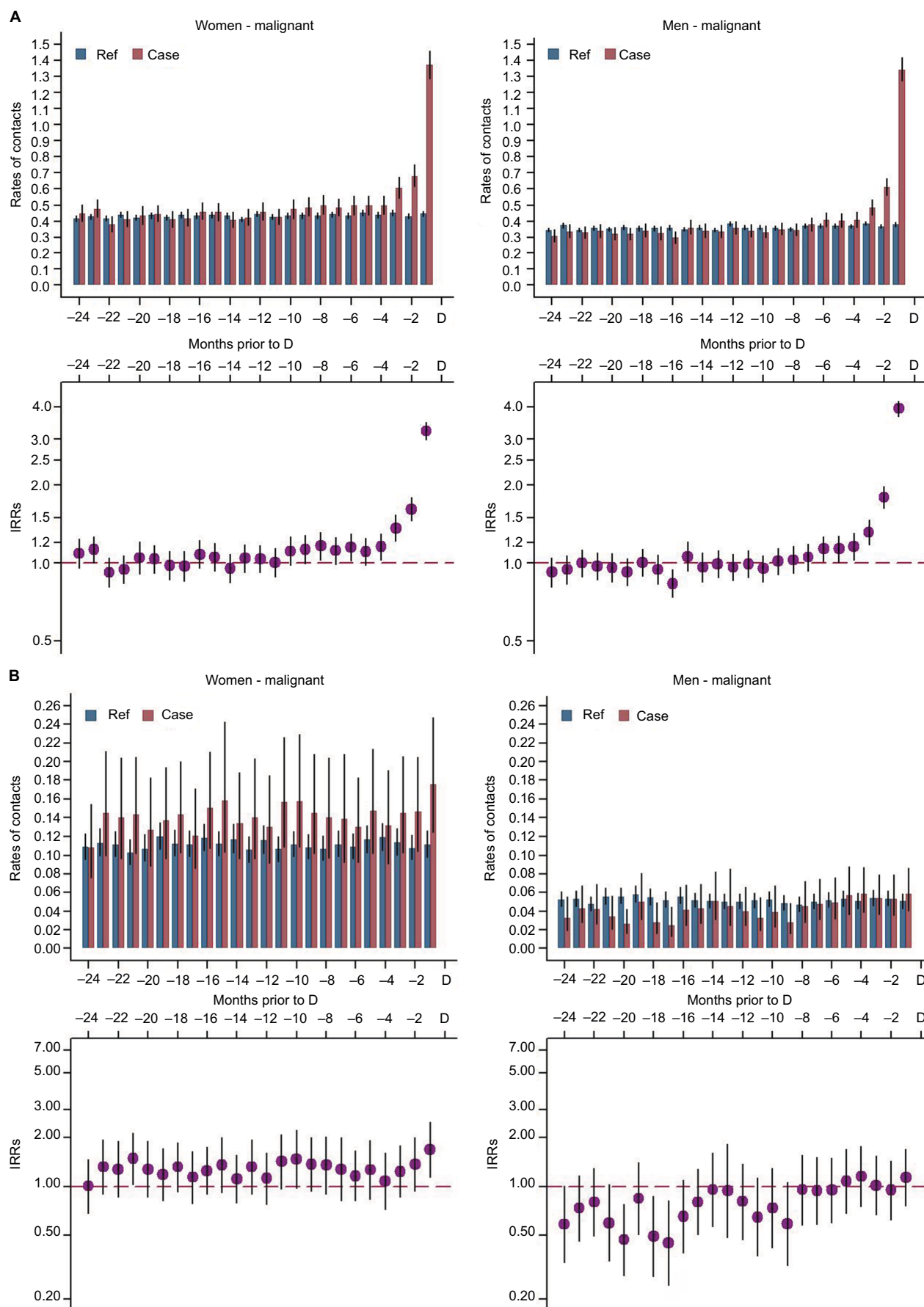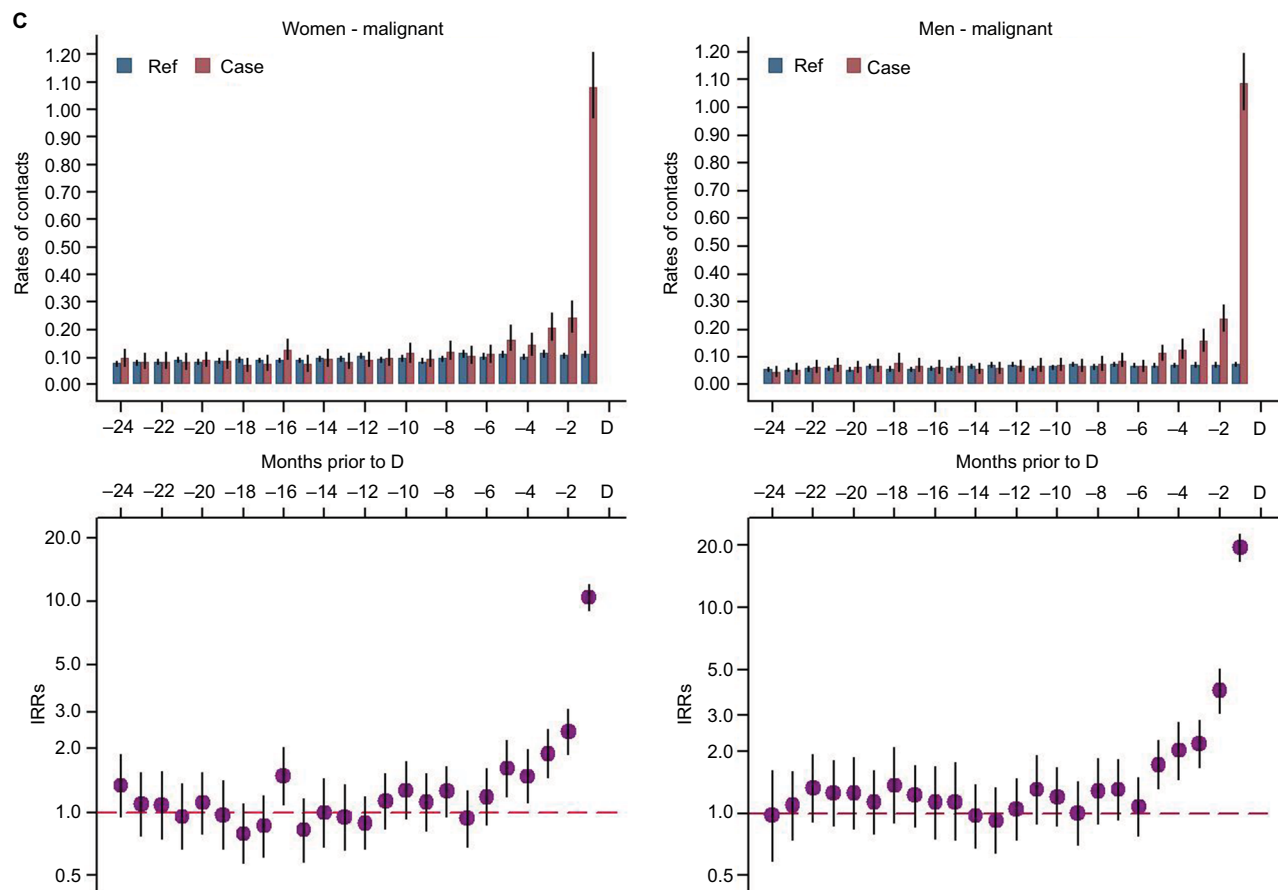
Figure 2 (*Continued*)

Figure 2 Total health care contacts to GP (daytime) (**A**) physiotherapy (**B**), and radiological examinations (**C**) among patients with malignant primary intracranial tumors.
Notes: Upper parts of **A–C**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A–C**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; GP, general practitioner; IRR, incidence rate ratio; Ref, reference.

increased alertness of health care professionals among patients with a previous history of cancer. This decreased the risk of confounding, but it may also have decreased the generalizability of the study. Surveillance bias may play a role as the patients had more known diseases requiring consultations with medical specialists than the comparison subjects (Table S2). Yet, the results only changed slightly after adjustment for known specialty-specific diseases (Tables 2 and S1).

Although the gender-specific analyses and the benign/malignant stratification procedure were used to acknowledge and limit the risk of confounding and selection bias, these analyses and procedures also reduced the statistical precision of the study.

For some of the outcomes, it may be argued that the individual risk of having an increased health care utilization is low, as the absolute difference in proportion is small despite a large relative difference. However, the population-based

estimates still indicate possible aspects of clinical practice, which may be optimized at the individual patient level.

Comparison with other studies

We could not compare our findings directly with other studies of health care use prior to a primary intracranial tumor diagnosis in adults due to the absence of such studies. However, studies in children and young adults with CNS tumors have found increased health care use from 6 and 17 months before diagnosis, respectively.[31,11] Yet, neither of these studies accounted for differences between benign and malignant tumors. Even so, our findings of increased health care use for patients with benign primary intracranial tumors for up to 2 years before diagnosis indicate that the possibility for an earlier diagnosis in adult patients with benign primary intracranial tumors may be larger than the window of opportunity found in children and young adults with CNS tumors.
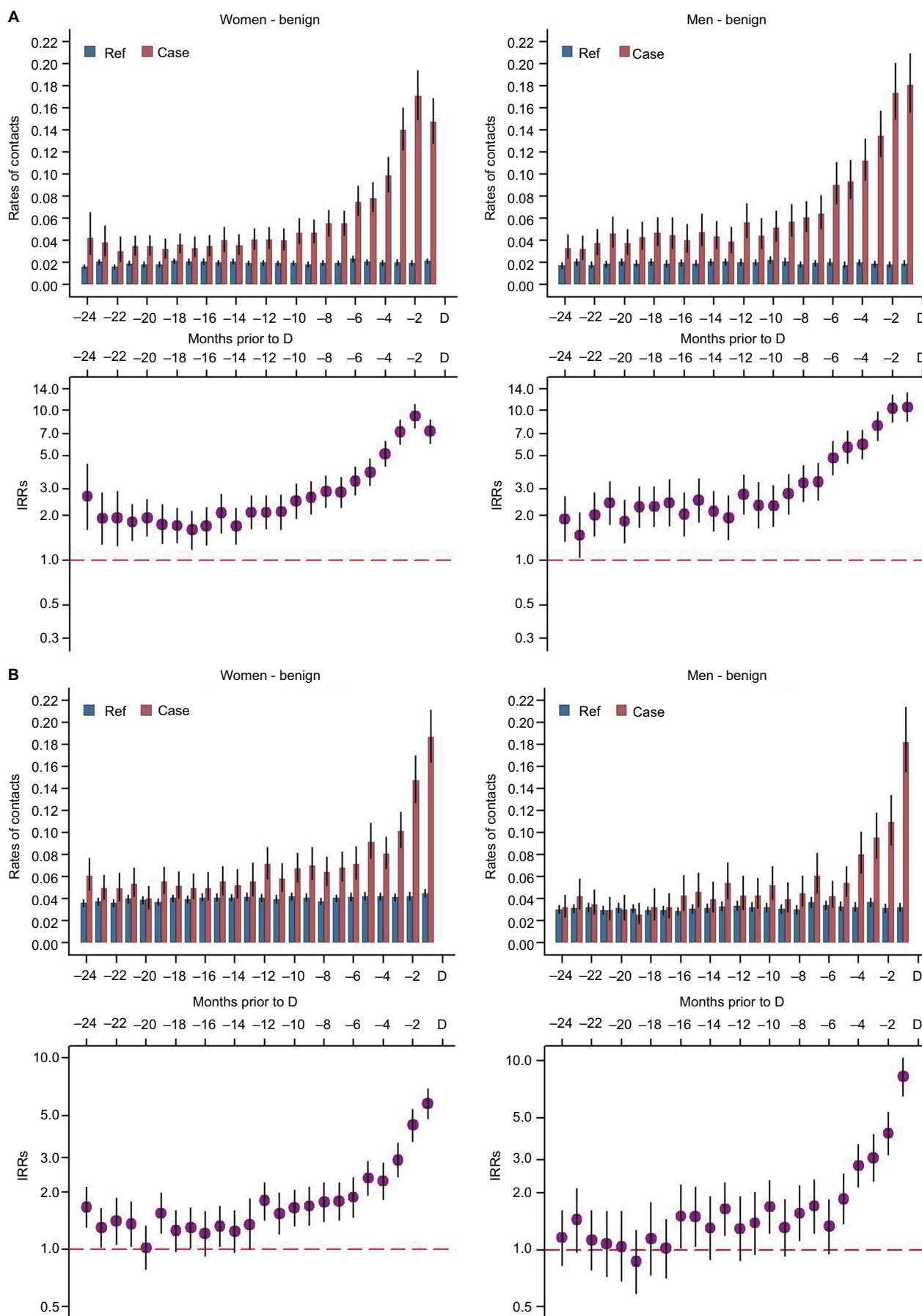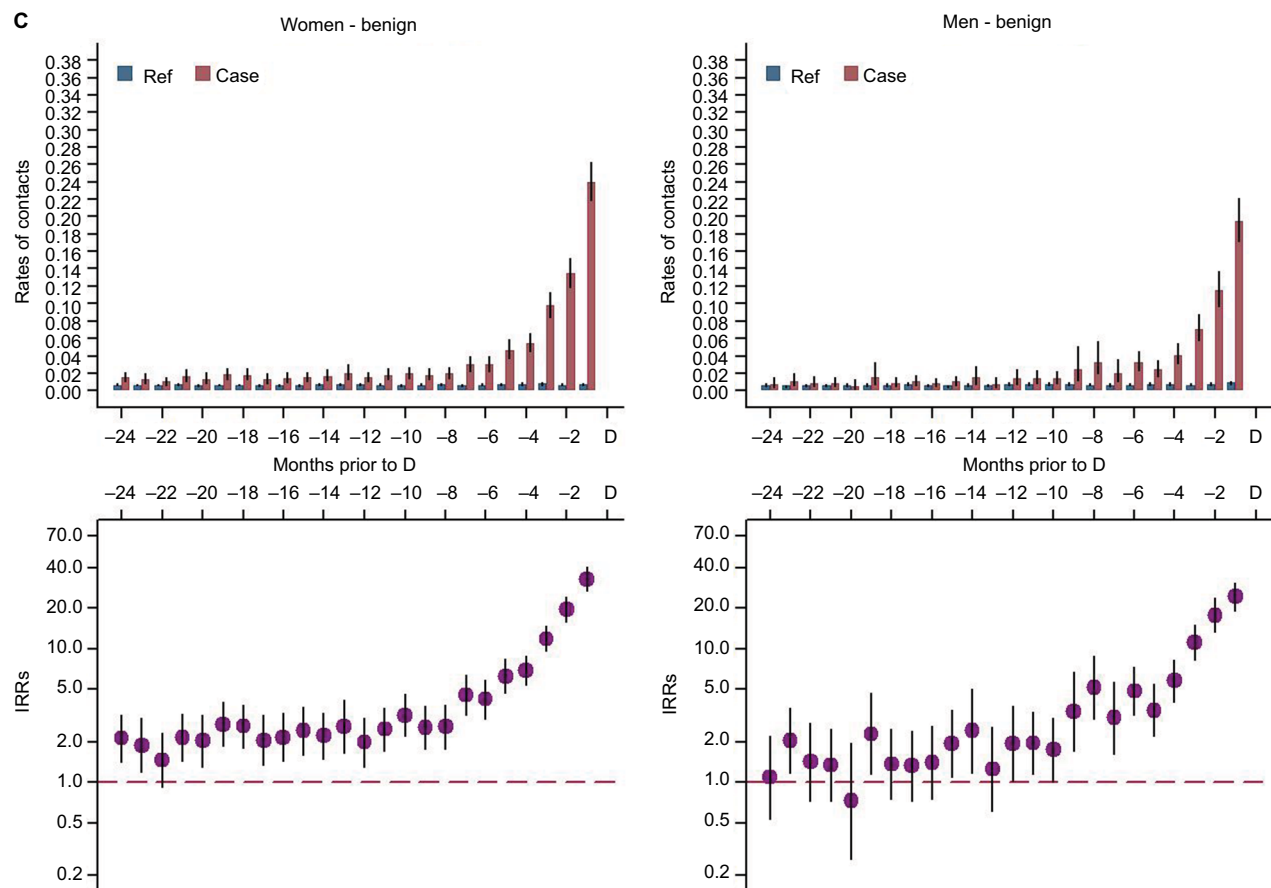
Figure 3 (*Continued*)

Figure 3 Total health care contacts to ENT (**A**), ophthalmology (**B**), and neurology (**C**) among patients with benign primary intracranial tumors.
Notes: Upper parts of **A–C**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A–C**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; ENT, ear–nose–throat; IRR, incidence rate ratio; Ref, reference.

Studies of other cancer types have reported increased health care use before a cancer diagnosis with a steep rise from 3 to 6 months prior to diagnosis.[32–34] Interestingly, 1 study found an increased health care use up to 2 years prior to diagnosis among lung cancer patients with known chronic obstructive pulmonary disease.[35] In contrast to these studies, we found that patients with malignant primary intracranial tumors only had an increase in health care use relatively close to the time of diagnosis, which indicates lower opportunity for an earlier diagnosis in this group of patients. Studies from the UK have shown that brain tumor patients are more likely to have multiple primary care consultations before referral to hospital[12] and to have long primary care intervals.[12,36] This may indicate that the symptomatology in patients with a primary intracranial tumor is more nonspecific and vague than in patients with other types of cancers.

In contrast to a Danish study,[37] the primary intracranial tumor patients in our study had almost the same amount of

psychiatric contacts than the comparison subjects. Female patients did, however, have significantly increased health care use from 4 months prior to diagnosis for benign tumors and from 2 months prior to diagnosis for malignant tumors; this is in accordance with the findings by Benros et al.[37]

It is well established that many patients with intracranial tumors present with first-time seizures or sudden onset of focal neurological symptoms.[7,38–41] Such emergency presentations could be a marker of diagnostic delay, but it could also simply be related to the nature of intracranial tumors.[42–44] Yet, it is ambiguous if these patients have had an initial symptomatic presentation in general practice that did not lead to suspicion of cancer.[37,41]

As many intracranial tumor patients present as emergencies and as most of the symptoms of intracranial tumors have low predictive values in general practice,[8,45,46] only about 1% of adult intracranial tumors are diagnosed following a fast-track GP referral for suspected cancer in the UK.[40] In Denmark, the number of patients detected through the Danish
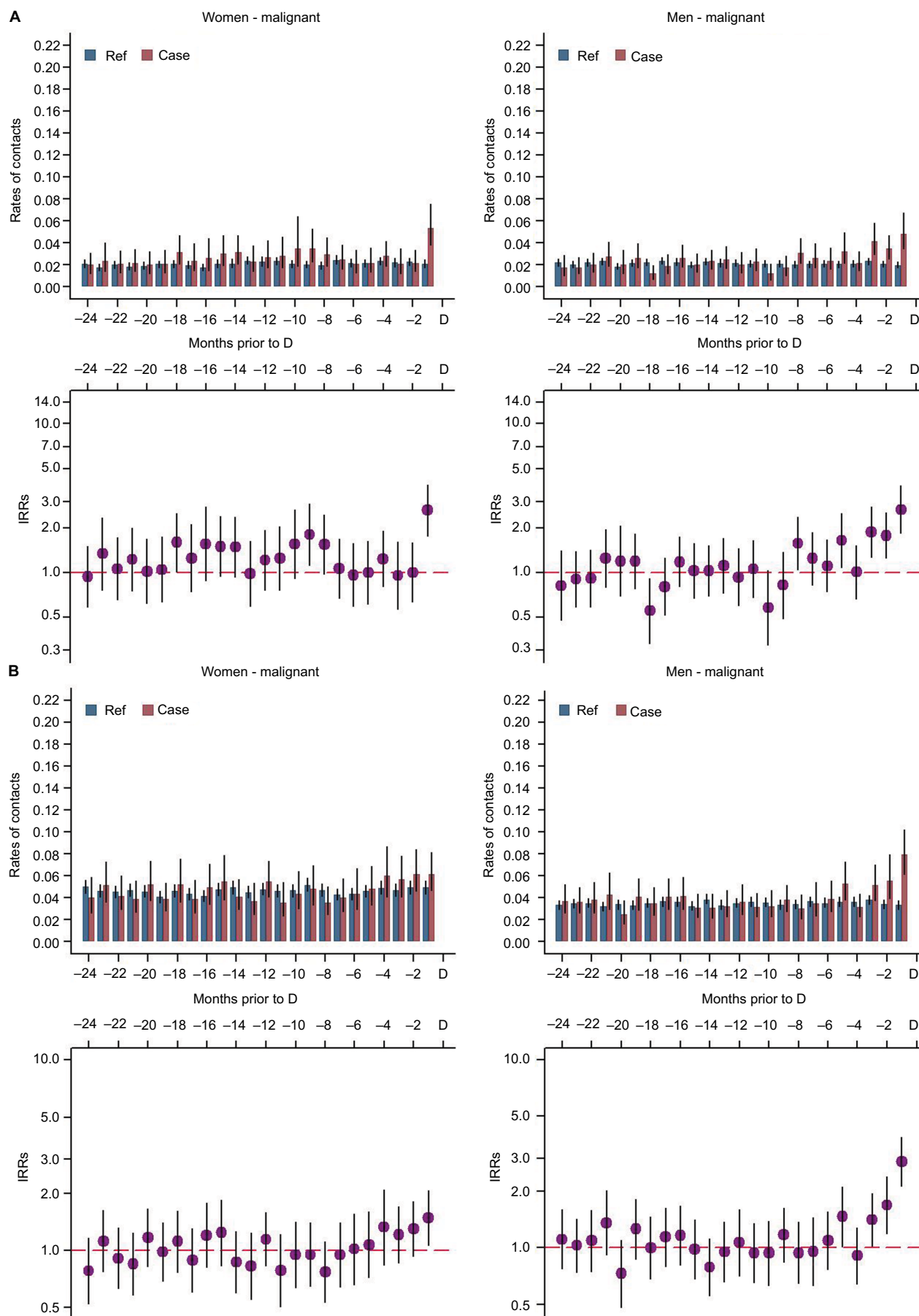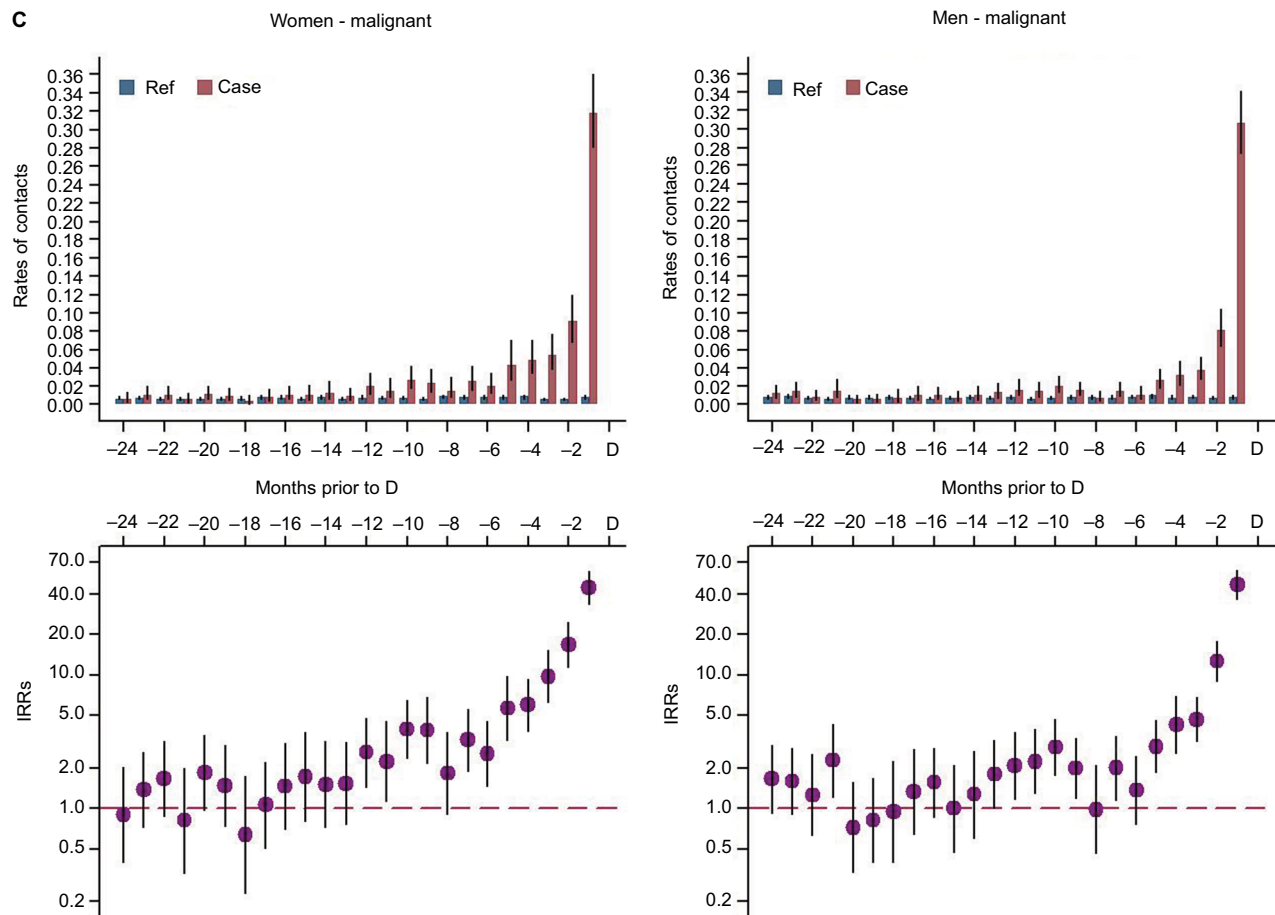
Figure 4 (*Continued*)

Figure 4 Total health care contacts to ENT (**A**), ophthalmology (**B**), and neurology (**C**) among patients with malignant primary intracranial tumors.
Notes: Upper parts of **A–C**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A–C**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; ENT, ear–nose–throat; IRR, incidence rate ratio; Ref, reference.

brain Cancer Patient Pathway is unknown, but more than one-third of the patients diagnosed with an intracranial tumor were initially referred on suspicion of other neurological illnesses.[45] Although the Danish brain Cancer Patient Pathway has been found to have acceptable diagnostic work-up time, our study indicates that the diagnosis may be achievable much sooner, as especially patients with a benign tumor have increased health care activity involving several medical specialists many months before diagnosis.

Conclusion

Patients diagnosed with benign and malignant primary intracranial tumors use health care services differently. The increased health care use seen among patients with benign primary intracranial tumors several months prior to diagnosis indicates that there may be a window of opportunity to diagnose these patients several months earlier. In contrast, for patients with malignant primary intracranial tumors, the

increased health care use occurred within relatively close proximity to the diagnosis, which indicates lower opportunity for earlier diagnosis in this group of patients.

Future studies should focus on the reasons behind the increased health care use before diagnosis for the patients diagnosed with a benign primary intracranial tumor in order to optimize the diagnostic process.

Acknowledgments

funding sources had a role in the design, conduct, analysis, or reporting of the study.

Disclosure

The authors report no conflicts of interests in this work.

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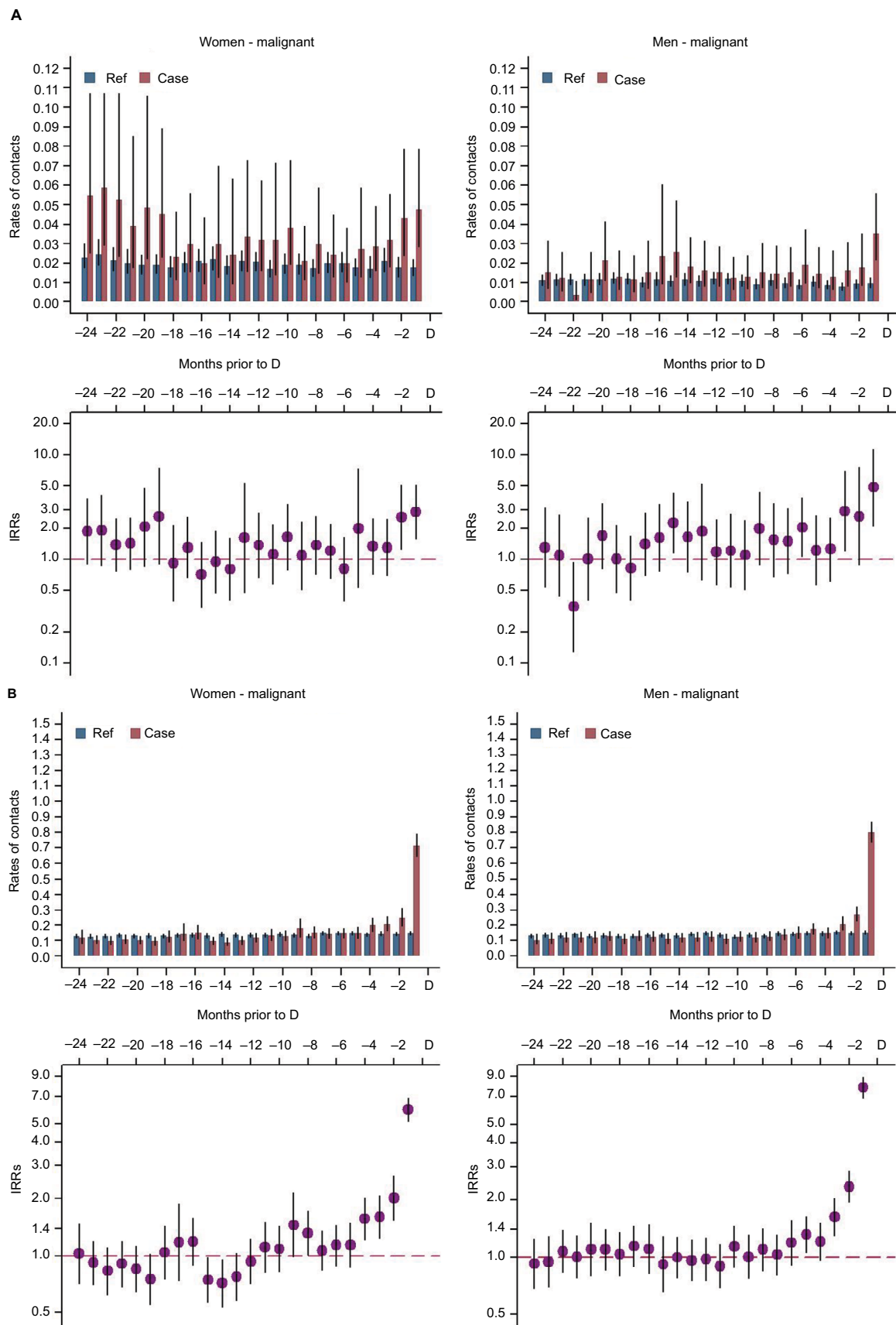
Supplementary materials

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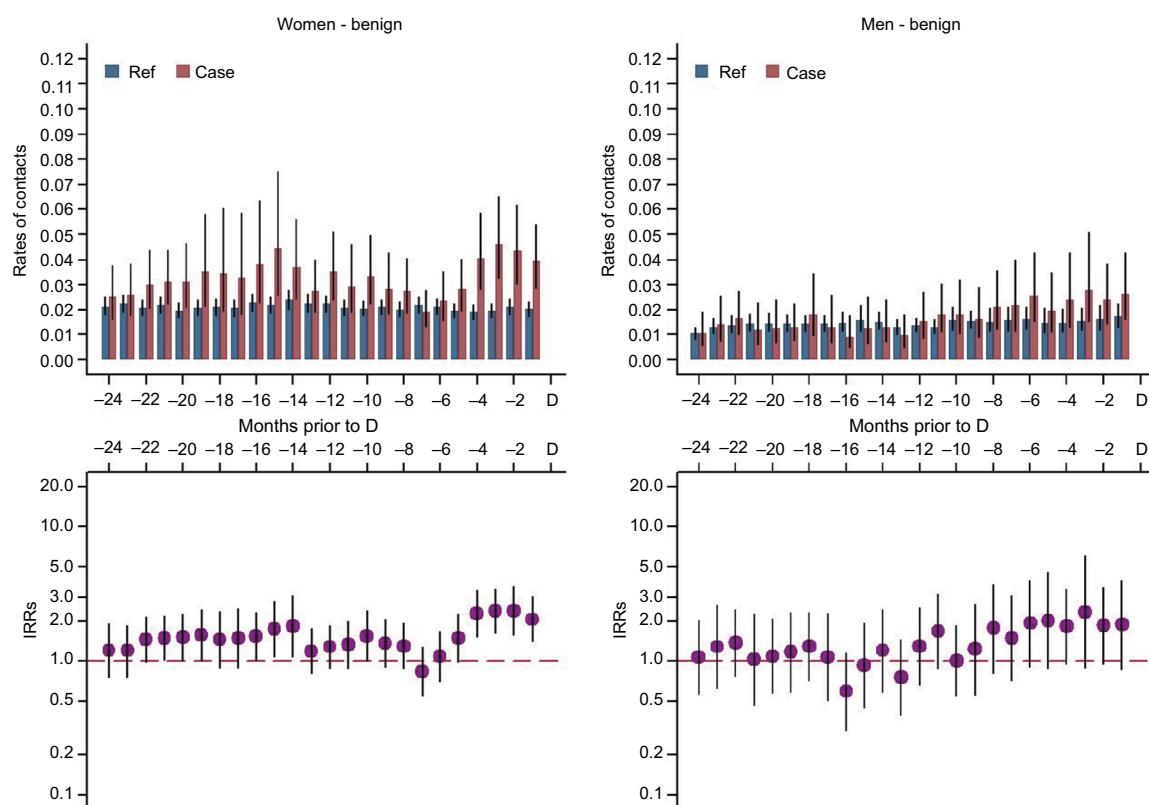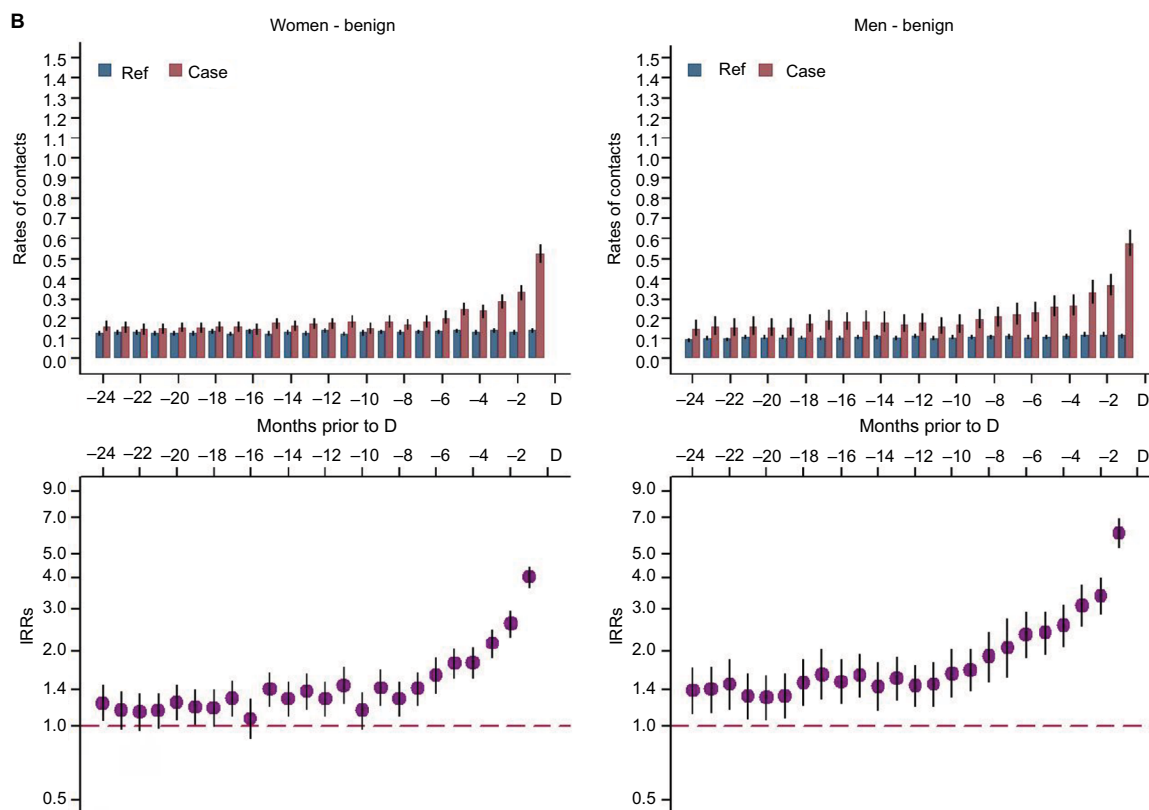
Figure S1 Total health care contacts to psychiatry (**A**) and other hospital contacts (**B**) among patients with benign primary intracranial tumors.
Notes: Upper parts of **A** and **B**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A** and **B**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; IRR, incidence rate ratio; Ref, reference.

Figure S2 Total health care contacts to psychiatry (**A**) and other hospital contacts (**B**) among patients with malignant primary intracranial tumors.
Notes: Upper parts of **A** and **B**: average rates of contacts for patients and comparison subjects 24 months prior to diagnosis/index date. Lower parts of **A** and **B**: IRRs with 95% CIs.
Abbreviations: CI, confidence interval; D, date of diagnosis/index date; IRR, incidence rate ratio; Ref, reference.

Table S1 The associations between health care contacts and being diagnosed with a primary intracranial tumor

Benign tumors

Number of contacts by specialty	Women						Men					
	Patients		Comparison subjects		OR	95% CI	Patients		Comparison subjects		OR	95% CI
	n	%	n	%			n	%	n	%		
ENT												
0	1,791	80.8	19,677	88.8	0.54	0.48–0.61	1,157	80.5	12,826	89.2	0.52	0.45–0.61
1–2	279	12.6	1,816	8.2	1.57	1.36–1.81	177	12.3	1,120	7.8	1.57	1.32–1.88
≥3	146	6.6	667	3.0	2.13	1.74–2.61	104	7.2	434	3.0	2.29	1.79–2.95
Ophthalmology												
0	1,684	76.0	17,717	80	0.82	0.73–0.91	1,153	80.2	12,210	84.9	0.69	0.60–0.81
1–2	368	16.6	3,256	14.7	1.12	0.99–1.27	215	15.0	1,593	11.1	1.44	1.22–1.70
≥3	164	7.4	1,187	5.4	1.37	1.14–1.64	70	4.9	577	4.0	1.22	0.92–1.60
Neurology												
0	2,053	92.6	21,299	96.1	0.58	0.48–0.71	1,359	94.5	13,842	96.3	0.78	0.59–1.03
1–2	102	4.6	652	2.9	1.42	1.12–1.80	59	4.1	395	2.7	1.32	0.98–1.80
≥3	61	2.8	209	0.9	2.39	1.66–3.44	20	1.4	143	1.0	1.14	0.66–1.97
Psychiatry												
0	2,137	96.4	21,444	96.8	1.06	0.81–1.39	1,394	96.9	14,056	97.7	0.70	0.48–1.01
1–2	19	0.9	216	1.0	0.72	0.43–1.21	19	1.3	100	0.7	2.04	1.16–3.57
≥3	60	2.7	500	2.3	1.05	0.77–1.43	25	1.7	224	1.6	1.16	0.72–1.88

Malignant tumors

Number of contacts by specialty	Women						Men					
	Patients		Comparison subjects		OR	95% CI	Patients		Comparison subjects		OR	95% CI
	n	%	n	%			n	%	n	%		
ENT												
0	816	85.8	8,315	87.4	0.92	0.75–1.13	1,169	88.5	11,641	88.1	1.14	0.94–1.38
1–2	99	10.4	902	9.5	1.06	0.84–1.33	103	7.8	1,121	8.5	0.84	0.68–1.05
≥3	36	3.8	293	3.1	1.11	0.75–1.63	49	3.7	448	3.4	0.95	0.68-1.33
Ophthalmology												
0	727	76.4	7,357	77.4	0.92	0.78–1.08	1,099	83.2	10,924	82.7	1.01	0.87–1.19
1–2	159	16.7	1,547	16.3	1.05	0.87–1.26	149	11.3	1,682	12.7	0.90	0.75–1.08
≥3	65	6.8	606	6.4	1.18	0.90–1.56	73	5.5	604	4.6	1.27	0.98–1.66
Neurology												
0	903	95.0	9,123	95.9	0.87	0.63–1.20	1,253	94.9	12,695	96.1	0.77	0.59–1.02
1–2	30	3.2	296	3.1	0.82	0.56–1.21	54	4.1	377	2.9	1.41	1.05–1.91
≥3	18	1.9	91	1.0	2.44	1.42–4.19	14	1.1	138	1.0	0.98	0.55–1.76
Psychiatry												
0	922	97.0	9,225	97.0	0.97	0.64–1.48	1,297	98.2	12,936	97.9	1.08	0.67–1.74
1–2	7	0.7	94	1.0	0.72	0.31–1.71	<5	-	96	0.7	0.48	0.18–1.31
≥3	22	2.3	191	2.0	1.15	0.70–1.88	20	1.5	178	1.3	1.16	0.67–2.00

Notes: OR adjusted for known specialty-specific disease. Adjusted for country of origin, CCI, marital status, income, labor market affiliation, highest educational level, and known specialty-specific disease.
Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ENT, ear–nose–throat; OR, odds ratio.

Table S2 Proportion of patients and comparison subjects with known disease 10 years before study entry (before 2 years prior to date of diagnosis/index date)

Benign tumors

Disease category	Patients with disease		Comparison subjects	
	%	n	%	n
Headache and migraine[a]	1.7	62	1.2	426
Epilepsy[b]	2.1	75	0.9	327
ENT disease[c]	11.4	417	7.6	2,789
Ophthalmologic disease[d]	12.9	470	10.6	3,869
Neurological disease excluding epilepsy, etc.[e]	9.7	353	6.4	2,351
Psychiatric disease excluding dementia[f]	5.4	198	4.4	1,596
Neurological disease[g]	11.1	407	7.1	2,607

Malignant tumors

Disease category	Patients with disease		Comparison subjects	
	%	n	%	n
Headache and migraine[a]	0.5	11	0.9	212
Epilepsy[b]	2.0	45	0.9	208
ENT disease[c]	11.8	268	9.6	2,177
Ophthalmologic disease[d]	11.0	249	11.7	2,656
Neurological disease excluding epilepsy, etc.[e]	6.6	150	6.5	1,481
Psychiatric disease excluding dementia[f]	4.3	97	4.3	968
Neurological disease[g]	8.1	184	7.2	1,639

Notes: [a]Headache and migraine (G43;G44); [b]epilepsy: (G40); [c]ENT disease: disease in ear and mastoid process of temporal bone (H60-H95); [d]ophthalmologic disease: diseases in eye and orbital region (H00-H59); [e]neurological disease (G00-G99) excluding epilepsy, migraine, headache, and neurological disease in the CCI, cerebrovascular disease (G45;G46), hemiplegia (G81;G82), dementia (G30); [f]psychiatric disease excluding dementia, psychiatric disease, and behavioral disorders (F03-F05.0 and F05.2-F99) excluding F00-F03; F05.1; [g]neurological disease excluding neurological disease in the CCI.
Abbreviations: CCI, Charlson Comorbidity Index; ENT, ear–nose–throat.