

Archives of  
**Disease in Childhood**

**Childhood cancer, type 1 diabetes, and other immune diseases: Healthcare visits in the year before diagnosis in Taiwan**

Journal:	<i>Archives of Disease in Childhood</i>
Manuscript ID	archdischild-2016-311762.R2
Article Type:	Original article
Edition:	not in use
Date Submitted by the Author:	n/a
Complete List of Authors:	Yang, TienYu; University of Oxford, Nuffield Department of Population Health Huang, Wan-Ting; Taiwan Centers for Disease Control, Office of Preventive Medicine Chen, Mei-Huei; National Taiwan University Hospital Yun-Lin Branch, Department of Pediatrics Huang, Kuan-Ying Arthur; Chang Gung Memorial Hospital, Chen, Pau-Chung; National Taiwan University College of Public Health, Institute of Occupational Medicine and Industrial Hygiene and Department of Public Health; National Taiwan University College of Medicine and Hospital, Department of Environmental and Occupational Medicine
Keywords:	Health Service, childhood cancer, adolescent cancer, type 1 diabetes mellitus, immune diseases

SCHOLARONE™  
Manuscripts

**Childhood cancer, type 1 diabetes, and other immune diseases: Healthcare visits in the year before diagnosis in Taiwan**

TienYu Owen Yang, MD DPhil, Nuffield Department of Population Health, University of Oxford

Wan-Ting Huang, MD, Taiwan Centers for Disease Control

Mei-Huei Chen, MD PhD, Institute of Population Health Sciences, National Health Research Institutes

Kuan-Ying Arthur Huang, MD PhD, Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Memorial Hospital

Pau-Chung Chen, MD PhD, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health; Department of Public Health, National Taiwan University College of Public Health; Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine and Hospital

**Correspondence to:**

Dr. TienYu Owen Yang,

Cancer Epidemiology Unit, Richard Doll Building, Old Road Campus, Oxford OX3 7LF United Kingdom

TEL: +44 (0) 1865289600

FAX: +44 (0) 1865289610

E-mail: [tienyu.owen.yang@gmail.com](mailto:tienyu.owen.yang@gmail.com)

## CONTRIBUTIONSHIP

TOY oversaw the study and was the primary analyst and the primary author of the manuscript. W-T H, M-H C, and K-Y H reviewed the manuscript and partook the process of interpretation and writing. M-H C and P-C C set up the infrastructure for data acquisition and data analysis. All authors had full access to statistical reports and tables in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

## FUNDING AND CONFLICT OF INTEREST

The study is funded internally by University of Oxford and National Taiwan University. There is no conflict of interest.

On behalf of co-authors, I (TienYu Owen Yang) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

## LICENCE FOR PUBLICATION STATEMENT

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive licence for UK Crown and US Federal Government employees) on a worldwide basis to the BMJ Publishing Group Ltd, and its Licensees to permit this article (if accepted) to be published in Archives of Disease in Childhood and any other BMJ PGL products and to exploit all subsidiary rights.

Word count: 2449

**WHAT IS KNOWN ABOUT THIS TOPIC**

Cancer, diabetes, and some immune diseases cause a large burden to children and family. These diseases have always been hoped to be diagnosed as soon as possible, but most diseases start with general presentations, at which stage a diagnosis cannot be confirmed or excluded immediately.

**WHAT THIS STUDY ADDS**

This study revealed two pictures of diagnostic difficulties at least in Taiwan. Children with underlying cancer or immune diseases (except diabetes) could take months to achieve a diagnosis despite many children did have typical presentations. By contrast, the diagnosis of diabetes is generally quick but many already had ketoacidosis when children first saw their doctors.

## ABSTRACT

### Background

Cancer, type 1 diabetes, and other immune diseases are often presented initially with non-specific problems. For how long children have been seeking medical help before the diagnosis is relatively unknown.

### Methods

During 2002-2013, 7238 children at ages 2-15 years diagnosed with cancer of 7 sites, type 1 diabetes, and 3 other immune diseases were registered in the Taiwan National Health Insurance Catastrophic Illness Database. Their healthcare visit records in the year prior to diagnosis were extracted and compared to the records of matched controls during comparable periods using mixed-effect models.

### Results

Except for diabetes, there were substantial increases in healthcare visit rates in the last few months before diagnosis of cancer or immune conditions, suggesting that some children had been seeking medical help and it had taken months to achieve a diagnosis. Many recorded presentations during this time were consistent with typical manifestations of the underlying condition, such as increasing apparent injuries prior to the diagnosis of bone cancer (6.6 folds increase in recent 4 months, 95% confidence interval 4.9-9.0). Comparatively, healthcare visits in the year prior to the diagnosis of diabetes were less common, but at the time of diagnosis 64% (1504/2335) children were presented with diabetes ketoacidosis.

### Conclusion

Many children with cancer or immune diseases, even with typical presentations, still required a period of time to confirm the diagnosis. By contrast, children with type 1 diabetes did not typically visit doctors until ketoacidosis occurred.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Keywords:** health service; childhood cancer; adolescent cancer; type 1 diabetes mellitus; immune diseases

Confidential: For Review Only

## INTRODUCTION

Cancer, type 1 diabetes, and other immune disorders are main debilitating physical conditions in childhood after the perinatal period. These diseases are rare but bring a large burden to the children and the family, and the diagnosis would ideally be confirmed or excluded as soon as possible.

However, many conditions start with general presentations (e.g. low grade fever), at which stage an immediate diagnosis of underlying conditions may not always be possible.

How long children had been seeking medical help before diagnosis is under-reported. A case-only study on childhood brain tumour in the UK <sup>1</sup> and our recent case-control study on childhood leukaemia in Taiwan <sup>2</sup> both reported increasing rates of healthcare visits months before the diagnosis. To our knowledge there have not been reports for other diseases. In this report we summarised children's healthcare visits in the year before the diagnosis of 11 conditions in Taiwan, including cancer of 7 sites, type 1 diabetes, and 3 other immune diseases. We also described the variety of common general presentations seen by physicians in these visits.

## METHODS

The matched nested case-control study was based on healthcare visit records in two Taiwan National Health Insurance Research Databases (NHIRD),<sup>3</sup> the NHIRD Longitudinal Database 2005 and the NHIRD Catastrophic Illness database 1998-2013. The NHIRD Longitudinal Database 2005 took a 1-million random sample of Taiwanese population (~4% of 23 million) in 2005, and the NHIRD Catastrophic Illness database 1998-2013 included all Taiwanese people who had a debilitating physical and mental condition, who were registered in the health insurance system (>99% coverage in Taiwan) and were subject to substantial reimbursement. In both databases, clinical impressions of all inpatient (hospital admissions) and outpatient healthcare (emergency or clinic visits) episodes were recorded by physicians according to the International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9) since 2000.

The two databases is effectively a nested case-control sample of the entire Taiwanese population. From the NHIRD Catastrophic Illnesses database, we included all children born in or before 2005, first diagnosed with 11 conditions between ages 2 and 15 years (inclusive) during 2002-2013, and matched each case with up to 5 controls from the NHIRD longitudinal 2005 database by calendar year and month of birth, sex, and region (northern, central, southern Taiwan and other)<sup>4</sup>, and an index date was assigned for each control on the date when the matched case was diagnosed.

*Health conditions and date of diagnosis*

Identified by ICD-9 codes, the 11 conditions included cancer of 7 sites (bone cancer 170.x, soft tissue cancer 171.x, ovarian cancer 183.0x, brain tumour 191.x, lymphoma 202.x, acute lymphoid leukaemia 204.x, and acute myeloid leukaemia 205.0x), type 1 diabetes (250.x), and 3 other immune diseases (myasthenia gravis 358.x, systemic lupus erythematosus 710.0x, and rheumatoid arthritis 714.0x). We also selected 2 registered debilitating conditions of external causes (severe burns 948.x and injuries 959.x) for comparisons. The date of diagnosis was defined as the visit date when the first near-diagnosis was recorded. For cancer cases the near-diagnoses included cancer diagnoses of all sites or neoplasm of unknown origin or behaviour. For burns and injuries these included all hospital admissions for external causes (ICD-9 codes 8XX and 9XX).

*Presentation-specific healthcare visits*

Six groups of clinical impressions were assigned according to ICD-9 codes to broadly represent apparent problems recorded in each healthcare visit, including respiratory problems (RESP, ICD-9 38X, 46X, 48X), atopic and immunologic problems (IM, ICD-9 473, 477, 493, 691, 708), gastrointestinal problems (GI, ICD-9 003, 008, 009, 53X, 54X, 558, 56X), urogenital problems (URO, ICD-9 58X-60X, 614-619, 62X), apparent injuries (INJ, ICD-9 681, 682, 8XX 90X-95X), and neuropsychosocial problems (NEURO, ICD-9 30X-35X). Symptomatic ICD-9 codes (780-789) such as fever or headache were not included.

*Data analysis*



Because only children born before 2006 were included in this study, the person-time included in this study was skewed to older ages. Age distribution (medians and interquartile ranges) of each condition was therefore described in a subsample in which all cases diagnosed on or after 2006 were excluded, so that the subsample was age-proportional for the entire post-perinatal child population (ages 2-15 years inclusive) in the country during 2000-2005. Age-standardised incidence rates in the Taiwanese population were estimated using numbers of cases and child-years at risk in each 1-year age stratum (equally weighted) between 2 and 15 years, applying a sampling ratio of 1:23 (~4%) when we extrapolated child-years at risks from the 1-million NHIRD Longitudinal Database 2005, as the population size in Taiwan was 23 million.

For each condition we modelled age-adjusted monthly rates of healthcare visits 1-12 months prior to the date of diagnosis as two quartic functions of time-to-diagnosis, one for cases and one for controls. Among matched controls the age-adjusted monthly rates were expected to be stable over time since the index dates were uneventful, except that the rates in the longer term prior to the index dates might be slightly higher because the healthcare access rates were higher among younger ages,<sup>5</sup> which effect was adjusted for but not perfectly. Among cases we expected gradual increases in healthcare visits before diagnosis. The quartic functions of time was therefore chosen to capture the expected stable healthcare visit rates in the medium term and a sharp increase in rates in the short term prior to diagnosis in cases, as well as a potential increase in rates as a result of imperfect adjustment for age in both cases and matched controls. Practically, dataset at the child-month level was analysed within each case-control strata using mixed-effect models (*melogit* and *mepoisson*, STATA 14.1) at the child-month level, with adjustment for attained age as a cubic function, and calendar year and calendar month in discrete categories. A longer period prior to diagnosis (1-24 months) were included enhance a stable tail. To facilitate comparisons across conditions of various age distributions, standardised rates were presented for each month prior to diagnosis, according to a standardised population at age 5 years in June 2004.

We explored whether recent increases only in outpatient healthcare visits prior to diagnosis was presentation-specific, as the numbers of inpatient healthcare visits were too small for stratification by

presentation. To further cope with smaller numbers of events after stratification by presentation-specific visits, we compared presentation-specific outpatient visits 1-4 versus 5-8 months prior to diagnosis in case-only analyses with the same adjustment sets described earlier in the mixed-effect models. We made all estimates with more than 15 events in each analysis and when convergence was achieved within 100 iterations. In the text the exact  $p$  value is quoted to indicate the likelihood of chance finding, while all confidence intervals are listed in eTables. A crude  $p$  of less than 0.05 (not corrected for multiple comparisons) was used for nominal statistical significance.

*Data access and ethics considerations*

Pseudonymised databases released from authorities for research use were used in this study. Databases should be accessed via Taiwan Ministry of Health and Welfare (<http://www.mohw.gov.tw/EN/Ministry/>). Background information and data protection of NHIRD can be found on NHIRD website.<sup>6</sup>

## RESULTS

During ~43 million person-years, 7238 cases across 11 debilitating conditions were first diagnosed at ages 2-15 years, as well as 1906 children debilitated by external causes (severe burns and injuries, selected as comparison conditions). As shown in Figure 1 (additional numerical details in eTable1), there was a large variation in age at diagnosis across 11 conditions, with a range of age-standardised incidence rates (age 2-15 years) from 3.1 new cases of ovarian cancer to 52.7 new cases of type 1 diabetes per million child-years. The estimated age-standardised incidences of various cancers were in line with the reports from Taiwan Cancer Registry during the overlapping ages and years.<sup>7</sup>

Smoothed time-dependent curves suggested a relatively stable rate of healthcare visits among the background population after adjustment for attained age and calendar year and month (Figure 1 top row). Of children with 11 conditions (Figure 1, with additional numerical details listed in eTable2), the baseline rates of healthcare visits were also relatively stable and similar to the background population at least between the 12<sup>th</sup> and the 6<sup>th</sup> months before diagnosis. One to several months before the date of diagnosis, there had been substantial increases in the rates of outpatient healthcare visits, and to a lesser extent of inpatient healthcare visits. Exceptionally, we noticed the increasing rate of healthcare visit prior to the diagnosis of type 1 diabetes was substantially smaller compared to the other 10 diseases. We also noticed that of 2335 children with type 1 diabetes in this analysis, 1504 (64%) children had diabetic ketoacidosis when they were first diagnosed with diabetes.

The two comparison conditions represented two distinct age groups, i.e. severe burns were predominantly seen among younger children and severe injuries among older children. As expected, there was no evidence of increasing healthcare visit rates prior to these diagnoses.

For children diagnosed with the 11 conditions, we examined presentation-specific healthcare visits that were recently increased 1-4 months prior to the diagnosis compared to 5-8 months prior to diagnosis. Figure 2 shows statistically acceptable estimates, whilst full numerical details are listed in eTable3. The types of presentation-specific healthcare visits varied substantially by underlying condition. Organ-specificity of recorded presentations was seen across 4 solid tumours -- compared

to other presentations, recent increases were seen in apparent injuries (INJ) most strongly shortly prior to the diagnosis of bone cancer<sup>8</sup> (6.6 folds, 95% confidence interval [CI] 4.9-9.0) and of soft tissue cancer (4.1 folds, 95%CI 2.6-6.3); recent increases were seen in urogenital problems (URO) most strongly shortly prior to the diagnosis of ovarian cancer (3.5 folds, 95%CI 2.0-6.1); recent increases were seen in neuropsychosocial problems (NEURO, 3.4 folds, 95%CI 2.9-4.1) most strongly shortly prior to the diagnosis of brain tumour.<sup>1</sup> By contrast, it seemed that urogenital problems and apparent injuries were more commonly seen shortly prior to the diagnosis of more systematically involved diseases, including the three haematological malignancies, type 1 diabetes, systematic lupus erythematosus, and rheumatoid arthritis. Likely due to the small number of cases, there was no significant evidence of presentation-specific healthcare visits shortly prior to myasthenia gravis.

## DISCUSSION

In this study all-cause and presentation-specific healthcare visits in the year before the diagnosis of 11 conditions in Taiwanese children were investigated. For children with all conditions except diabetes, the rates of all-cause healthcare visits increased substantially months before diagnosis. For diabetes the increases in healthcare visits were comparably small prior to diagnosis.

These findings revealed a clinical reality and depicted how long on average it had taken for a diagnosis to be made since children had started to seek medical help. Among the 10 conditions including cancer of 7 sites and 3 immune diseases, recent increases (>3 folds) in organ-specific presentations shortly prior to the diagnosis of bone cancer,<sup>8</sup> soft tissue cancer, ovarian cancer,<sup>9</sup> and brain tumour,<sup>1</sup> and general presentations (urogenital problems and apparent injuries) at least prior to the diagnosis of lymphoma,<sup>10</sup> acute lymphoid leukaemia,<sup>2</sup> and systemic lupus erythematosus<sup>11</sup> were generally in line with known clinical presentations of each condition. This may suggest children with known presentations were missed in these clinic visits. However, it is also noteworthy that the background incidence rates of these conditions were low, at ~160 new cases of the 11 conditions combined per million child-years, and therefore several folds of increases in rates were unlikely to translate into a large increase in absolute risk (e.g. 10 folds increase would only translate into approximately 1.6 new case per 1000 child-years, or 0.0016% children in the year following these presentation-specific healthcare visits). Without more specific clinical findings, the vast majority of children with these clinical impressions are not expected to have severe conditions. Doctors, children, and families may be better communicated if this clinical reality is well informed.

We do not think that the lack of healthcare visits prior to the diagnosis of type 1 diabetes suggests that diabetes had been satisfactorily diagnosed, but instead it reiterates the challenges in diagnosing childhood type 1 diabetes in the community before ketoacidosis occurs. It was reported in the Pediatric Diabetes Consortium that 34% of children with type 1 diabetes were presented with ketoacidosis when they were newly diagnosed.<sup>12</sup> In our report it had been 64% in Taiwan during these years. The increase in healthcare visit rates prior to diagnosis was not obvious, and there were no

strong association ( $>3$  fold recent increase or baseline case-control difference) with any of the 6 presentation-specific healthcare visits, and with the largest number of diabetic cases among 11 conditions this lack of association cannot be largely explained by lack of statistical power.

Interpretation of our findings is limited by a number of factors. The uniform format used to summarise pre-diagnostic healthcare visits across various conditions provided a platform for cross-condition comparison, but this approach could under-estimate the heterogeneity by age and by background incidences of conditions. There could also be heterogeneity within each broadly assigned clinical impression category that cannot be taken into account in this report. Diagnosis of rheumatoid arthritis required a minimal symptomatic duration in order to fulfil diagnostic criteria ( $> 6$  weeks)<sup>13</sup> even when the diagnosis had been suspected. Many strong presentation-specific associations were consistent with known presentations of each condition, but some others cannot be easily explained by known knowledge especially when the association was weaker, and with a large number of estimates some findings could be due to chance.

With the high healthcare access in Taiwan (every 6 in 10 young children visit doctors every month on average)<sup>4</sup> and with centralised healthcare system that requires physicians to record clinical impressions according to a standard coding system (ICD-9), this is the largest data so far using which the prospectively collected healthcare records among children with debilitating conditions can be tracked backwards in time. Due to data availability and diagnostic validity we only restricted our analyses to the most common physical conditions registered in the Catastrophic Illness Database, but this list of conditions have captured the most common primary long-term debilitating physical conditions in the developed world. Even with the entirety of the data and the broad categories of presentations investigated, the numbers of healthcare visit episodes were still insufficient for some estimates. There are other countries in which this type of healthcare database is available or partially available for parallel investigation. We expect attempts from other countries to generalise or localise our findings across populations where disease prevalence and disease-detecting practices should differ.

1  
2  
3 In all, this report revealed two pictures of healthcare visits in the year prior to 11 debilitating  
4 conditions. Many children with cancer or immune diseases, even with organ-specific presentations,  
5  
6 still required one to several months to confirm the diagnosis, and this clinical reality may need to be  
7  
8 better communicated between doctors, children, and family. By contrast, children with type 1 diabetes  
9  
10 did not typically visit doctors until ketoacidosis occurred.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

REFERENCE

1. Chu TP, Shah A, Walker D, et al. Pattern of symptoms and signs of primary intracranial tumours in children and young adults: a record linkage study. Arch Dis Child 2015;**100**(12):1115-22.

2. Yang TO, Liu YL, Huang WT, et al. Specific and Non-specific Clinical Presentations in the Year Before the Diagnosis of Childhood Leukaemia. Pediatr Blood Cancer 2016;**63**(8):1387-93.

3. Hsing AW, Ioannidis JP. Nationwide Population Science: Lessons From the Taiwan National Health Insurance Research Database. JAMA internal medicine 2015;**175**(9):1527.

4. Yang TYO, Huang W-T, Chen M-H, et al. Seasonal synchrony in incidences of common infectious diseases in early childhood among neighbouring regions. International Journal of Infectious Diseases 2014;**28**:214.

5. Yang TO, Huang WT, Chen MH, et al. Diagnostic uncertainty of herpangina and hand-foot-and-mouth disease and its impact on national enterovirus syndromic monitoring. Epidemiology and infection 2015:1-8.

6. National Health Insurance Research Database: Data Protection. [updated November 2015]. Available from: [http://nhird.nhri.org.tw/en/Data\\_Protection.html](http://nhird.nhri.org.tw/en/Data_Protection.html).

7. Liu YL, Lo WC, Chiang CJ, et al. Incidence of cancer in children aged 0-14 years in Taiwan, 1996-2010. Cancer Epidemiol 2015;**39**(1):21-8.

8. Salunke AA, Chen Y, Tan JH, et al. Does a pathological fracture affect the prognosis in patients with osteosarcoma of the extremities? : a systematic review and meta-analysis. Bone Joint J 2014;**96-B**(10):1396-403.

9. Baert T, Storme N, Van Nieuwenhuysen E, et al. Ovarian cancer in children and adolescents: A rare disease that needs more attention. Maturitas 2016;**88**:3-8.

10. Hochberg J, El-Mallawany NK, Abila O. Adolescent and young adult non-Hodgkin lymphoma. British journal of haematology 2016;**173**(4):637-50.

11. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus 2011;**20**(13):1345-55.

12. Klingensmith GJ, Tamborlane WV, Wood J, et al. Diabetic ketoacidosis at diabetes onset: still an all too common threat in youth. The Journal of pediatrics 2013;**162**(2):330-4 e1.

13. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism 2010;**62**(9):2569-81.



## FIGURE LEGENDS

### **Figure 1. Healthcare visit rates in the year before the final diagnosis of 11 childhood debilitating physical conditions.**

For each condition, medians and interquartile ranges (IQR) of ages at diagnosis are shown in grey bars, and smoothed monthly rates of outpatient and inpatient healthcare visits in the year before diagnosis are presented in shades. The estimates and 95% confidence intervals (CI) for the last month before diagnosis were listed. Numbers and confidence intervals are listed in eTable2.

### **Figure 2. Increases in presentation-specific outpatient healthcare visit rates in the recent 4 months**

For each condition, the figure shows folds of recent increases in monthly rates of the 6 presentation-specific outpatient healthcare visits in the recent 4 months prior to diagnosis (cases only). Only estimates that are statistically acceptable are shown, defined by >15 events in each analysis, convergence within 100 iterations, and  $p < 0.05$ . Further numerical details including numbers and confidence intervals are listed in eTable3. Presentation-specific healthcare visits are coded by physicians at the conclusion of each visit and include respiratory problems (RESP, ICD-9 38X, 46X, 48X), atopic and immunologic problems (IM, ICD-9 473, 477, 493, 691, 708), gastrointestinal problems (GI, ICD-9 003, 008, 009, 53X, 54X, 558, 56X), urogenital problems (URO, ICD-9 58X-60X, 614-619, 62X), apparent injuries (INJ, ICD-9 681, 682, 8XX 90X-95X), and neuropsychosocial problems (NEURO, ICD-9 30X-35X). \* $p < 0.01$ ; \*\* $p < 0.001$ ; \*\*\*  $p < 0.0001$ ; \*\*\*\*  $p < 0.00001$

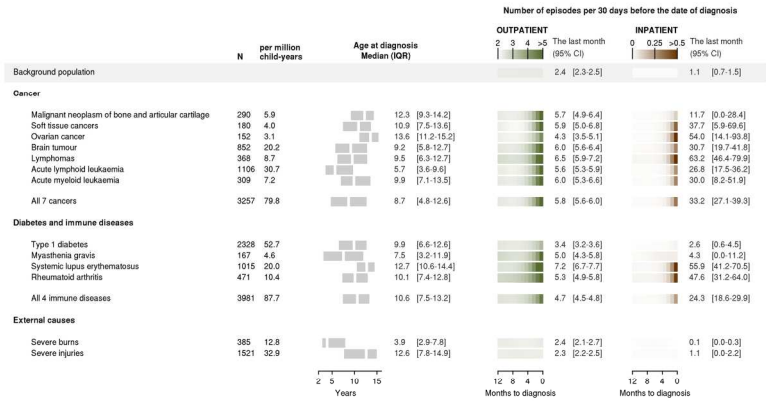


Figure 1. Healthcare visit rates in the year before the final diagnosis of 11 childhood debilitating physical conditions. For each condition, medians and interquartile ranges (IQR) of ages at diagnosis are shown in grey bars, and smoothed monthly rates of outpatient and inpatient healthcare visits in the year before diagnosis are presented in shades. The estimates and 95% confidence intervals (CI) for the last month before diagnosis were listed. Numbers and confidence intervals are listed in eTable2.

Figure 1  
203x135mm (300 x 300 DPI)

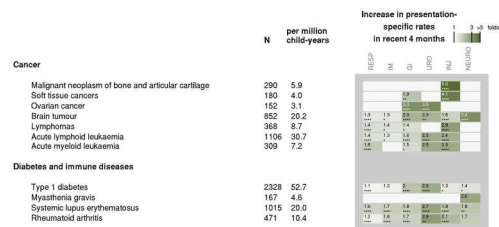


Figure 2. Increases in presentation-specific outpatient healthcare visit rates in the recent 4 months. For each condition, the figure shows folds of recent increases in monthly rates of the 6 presentation-specific outpatient healthcare visits in the recent 4 months prior to diagnosis (cases only). Only estimates that are statistically acceptable are shown, defined by >15 events in each analysis, convergence within 100 iterations, and  $p < 0.05$ . Further numerical details including numbers and confidence intervals are listed in eTable3. Presentation-specific healthcare visits are coded by physicians at the conclusion of each visit and include respiratory problems (RESP, ICD-9 38X, 46X, 48X), atopic and immunologic problems (IM, ICD-9 473, 477, 493, 691, 708), gastrointestinal problems (GI, ICD-9 003, 008, 009, 53X, 54X, 558, 56X), urogenital problems (URO, ICD-9 58X-60X, 614-619, 62X), apparent injuries (INJ, ICD-9 681, 682, 8XX 90X-95X), and neuropsychosocial problems (NEURO, ICD-9 30X-35X). \* $p < 0.01$ ; \*\* $p < 0.001$ , \*\*\* $p < 0.0001$ , \*\*\*\* $p < 0.00001$ .

Figure 2  
203x135mm (300 x 300 DPI)

Childhood cancer, type 1 diabetes, and other immune diseases:

Healthcare visits in the year before diagnosis in Taiwan

TienYu Owen Yang, Wan-Ting Huang, Mei-Huei Chen, Kuan-Ying Arthur Huang, and  
Pau-Chung Chen

Online Only Material

	Content	Page
<b>eTable1</b>	<b>Median ages and interquartile ranges corresponding to Figure 1</b>	<b>2</b>
<b>eTable2</b>	<b>Numbers and confidence intervals corresponding to Figure 1</b>	<b>3</b>
eTable2-1	Malignant neoplasm of bone and articular cartilage	3
eTable2-2	Soft tissue cancers	3
eTable2-3	Ovarian cancer	4
eTable2-4	Brain tumour	4
eTable2-5	Lymphomas	5
eTable2-6	Acute lymphoid leukaemia	5
eTable2-7	Acute myeloid leukaemia	6
eTable2-8	Type 1 diabetes	6
eTable2-9	Myasthenia gravis	7
eTable2-10	Systemic lupus erythematosus	7
eTable2-11	Rheumatoid arthritis	8
eTable2-12	Severe burns	8
eTable2-13	Severe injuries	9
eTable2-14	All 7 cancers	9
eTable2-15	All 4 immune diseases	10
<b>eTable3</b>	<b>Numbers and confidence intervals corresponding to Figure 2</b>	<b>11</b>

**eTable1: Median ages and interquartile ranges corresponding to Figure 1**

	count	Incidence per million child-year	Age		
			25 <sup>th</sup> percentile	Median	75 <sup>th</sup> percentile
Malignant neoplasm of bone and articular cartilage	290	5.94	9.28	12.25	14.21
Soft tissue cancers	180	4.03	7.53	10.90	13.57
Ovarian cancer	152	3.08	11.18	13.57	15.25
Brain tumour	852	20.17	5.81	9.17	12.72
Lymphomas	368	8.66	6.29	9.51	12.74
Acute lymphoid leukaemia	1106	30.66	3.64	5.65	9.59
Acute myeloid leukaemia	309	7.23	7.05	9.87	13.46
Type 1 diabetes	2328	52.69	6.58	9.89	12.59
Myasthenia gravis	167	4.55	3.18	7.53	11.87
Systemic lupus erythematosus	1015	20.04	10.60	12.72	14.37
Rheumatoid arthritis	471	10.43	7.39	10.11	12.84
Severe burns	385	12.77	2.91	3.89	7.83
Severe injuries	1521	32.85	7.77	12.62	14.87
All 7 cancers	3257	79.77	4.81	8.68	12.61
All 4 immune diseases	3981	87.71	7.50	10.63	13.23

eTable2: Numbers and confidence intervals corresponding to Figure 1  
eTable2-1

Malignant neoplasm of bone and articular cartilage				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.7 (4.9-6.4)	2.3 (2.1-2.6)	0.12 (-0.05-0.28)	0.01 (-0.01-0.03)
2	4.3 (3.9-4.7)	2.4 (2.2-2.6)	0.06 (-0.01-0.13)	0.01 (0.00-0.02)
3	3.4 (3.2-3.7)	2.4 (2.2-2.6)	0.03 (0.00-0.07)	0.01 (0.00-0.02)
4	2.9 (2.7-3.2)	2.4 (2.2-2.6)	0.02 (0.00-0.04)	0.01 (0.00-0.02)
5	2.6 (2.4-2.9)	2.4 (2.2-2.6)	0.01 (0.00-0.03)	0.01 (0.00-0.02)
6	2.5 (2.2-2.7)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
7	2.4 (2.2-2.6)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
8	2.3 (2.1-2.5)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
9	2.3 (2.1-2.5)	2.4 (2.3-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
10	2.3 (2.1-2.5)	2.4 (2.3-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
11	2.4 (2.2-2.6)	2.5 (2.3-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
12	2.4 (2.2-2.6)	2.5 (2.3-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)

CI: confidence interval

eTable2-2

Soft tissue cancers				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.9 (5.0-6.8)	2.6 (2.2-2.9)	0.38 (0.06-0.70)	0.01 (-0.01-0.03)
2	4.2 (3.8-4.7)	2.5 (2.2-2.7)	0.17 (0.03-0.30)	0.01 (0.00-0.03)
3	3.3 (3.0-3.6)	2.4 (2.2-2.6)	0.07 (0.01-0.14)	0.01 (0.00-0.03)
4	2.7 (2.5-3.0)	2.4 (2.2-2.6)	0.04 (0.00-0.07)	0.01 (0.00-0.03)
5	2.4 (2.2-2.6)	2.3 (2.2-2.5)	0.02 (0.00-0.04)	0.01 (0.00-0.03)
6	2.2 (2.0-2.4)	2.3 (2.1-2.5)	0.01 (0.00-0.03)	0.01 (0.00-0.03)
7	2.1 (1.9-2.3)	2.3 (2.1-2.5)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
8	2.1 (1.9-2.3)	2.3 (2.1-2.5)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
9	2.1 (1.9-2.3)	2.3 (2.2-2.5)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
10	2.2 (2.0-2.4)	2.4 (2.2-2.5)	0.01 (0.00-0.01)	0.01 (0.00-0.02)
11	2.3 (2.0-2.5)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
12	2.3 (2.1-2.6)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)

CI: confidence interval

eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)

eTable2-3

**Ovarian cancer**

Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	4.3 (3.5-5.1)	2.2 (1.9-2.6)	0.54 (0.14-0.94)	0.01 (-0.01-0.04)
2	3.5 (3.0-4.0)	2.2 (1.9-2.5)	0.25 (0.03-0.46)	0.01 (-0.01-0.03)
3	3.0 (2.6-3.4)	2.2 (1.9-2.5)	0.10 (-0.01-0.21)	0.01 (0.00-0.03)
4	2.7 (2.3-3.0)	2.2 (2.0-2.4)	0.05 (-0.01-0.11)	0.01 (0.00-0.03)
5	2.5 (2.1-2.8)	2.2 (1.9-2.4)	0.02 (-0.01-0.06)	0.01 (0.00-0.03)
6	2.3 (2.0-2.6)	2.2 (1.9-2.4)	0.02 (-0.01-0.04)	0.01 (0.00-0.03)
7	2.2 (2.0-2.5)	2.2 (1.9-2.4)	0.01 (0.00-0.03)	0.01 (0.00-0.03)
8	2.2 (1.9-2.5)	2.2 (2.0-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.03)
9	2.2 (2.0-2.5)	2.2 (2.0-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.03)
10	2.2 (2.0-2.5)	2.2 (1.9-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.03)
11	2.3 (2.0-2.5)	2.2 (1.9-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.03)
12	2.3 (2.0-2.6)	2.2 (1.9-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.03)

CI: confidence interval

eTable2-4

**Brain tumour**

Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	6.0 (5.6-6.4)	2.4 (2.3-2.5)	0.31 (0.20-0.42)	0.00 (0.00-0.01)
2	4.6 (4.3-4.8)	2.4 (2.3-2.5)	0.15 (0.10-0.20)	0.01 (0.00-0.01)
3	3.7 (3.5-3.8)	2.4 (2.3-2.5)	0.08 (0.05-0.10)	0.01 (0.00-0.01)
4	3.1 (3.0-3.3)	2.4 (2.3-2.5)	0.04 (0.03-0.06)	0.01 (0.01-0.01)
5	2.8 (2.7-2.9)	2.4 (2.3-2.5)	0.03 (0.02-0.04)	0.01 (0.01-0.01)
6	2.6 (2.5-2.7)	2.4 (2.3-2.5)	0.02 (0.01-0.03)	0.01 (0.01-0.01)
7	2.5 (2.4-2.6)	2.4 (2.3-2.5)	0.02 (0.01-0.02)	0.01 (0.01-0.01)
8	2.4 (2.3-2.5)	2.4 (2.3-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
9	2.4 (2.3-2.5)	2.4 (2.3-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
10	2.4 (2.3-2.5)	2.4 (2.3-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
11	2.5 (2.4-2.6)	2.4 (2.3-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
12	2.5 (2.4-2.6)	2.4 (2.3-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)

CI: confidence interval

eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)  
eTable2-5

Lymphomas				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	6.5 (5.9-7.2)	2.5 (2.3-2.7)	0.63 (0.46-0.80)	0.01 (0.00-0.03)
2	4.8 (4.5-5.2)	2.5 (2.3-2.7)	0.29 (0.18-0.41)	0.01 (0.00-0.02)
3	3.9 (3.6-4.1)	2.5 (2.3-2.6)	0.12 (0.06-0.18)	0.01 (0.00-0.02)
4	3.3 (3.1-3.5)	2.5 (2.4-2.6)	0.06 (0.03-0.09)	0.01 (0.00-0.02)
5	2.9 (2.8-3.1)	2.5 (2.4-2.6)	0.03 (0.01-0.06)	0.01 (0.00-0.02)
6	2.7 (2.6-2.9)	2.5 (2.3-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)
7	2.6 (2.5-2.8)	2.5 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
8	2.6 (2.4-2.8)	2.5 (2.4-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
9	2.6 (2.4-2.8)	2.5 (2.4-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
10	2.6 (2.5-2.8)	2.5 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
11	2.7 (2.5-2.8)	2.5 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
12	2.7 (2.5-2.9)	2.5 (2.3-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)

CI: confidence interval

eTable2-6

Acute lymphoid leukaemia				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.6 (5.3-5.9)	2.4 (2.3-2.5)	0.27 (0.17-0.36)	0.01 (0.01-0.02)
2	4.2 (4.0-4.4)	2.4 (2.3-2.5)	0.11 (0.08-0.14)	0.01 (0.01-0.02)
3	3.4 (3.3-3.5)	2.4 (2.4-2.5)	0.05 (0.03-0.06)	0.01 (0.01-0.01)
4	2.9 (2.8-3.0)	2.4 (2.4-2.5)	0.02 (0.02-0.03)	0.01 (0.01-0.01)
5	2.6 (2.5-2.7)	2.4 (2.4-2.5)	0.02 (0.01-0.02)	0.01 (0.01-0.01)
6	2.4 (2.3-2.5)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
7	2.3 (2.2-2.4)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
8	2.3 (2.2-2.3)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
9	2.3 (2.2-2.3)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
10	2.3 (2.2-2.4)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
11	2.3 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
12	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)

CI: confidence interval



eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)  
eTable2-7

### Acute myeloid leukaemia

Month(s) before diagnosis	Outpatient Monthly visit (95% CI)		Inpatient Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	6.0 (5.3-6.6)	2.5 (2.3-2.7)	0.30 (0.08-0.52)	0.02 (0.00-0.05)
2	4.5 (4.1-4.8)	2.4 (2.2-2.6)	0.11 (0.04-0.19)	0.02 (0.00-0.03)
3	3.6 (3.4-3.9)	2.4 (2.2-2.5)	0.05 (0.01-0.08)	0.01 (0.00-0.02)
4	3.1 (2.9-3.3)	2.3 (2.2-2.5)	0.02 (0.00-0.04)	0.01 (0.00-0.02)
5	2.7 (2.5-2.9)	2.3 (2.2-2.4)	0.01 (0.00-0.03)	0.01 (0.00-0.02)
6	2.5 (2.4-2.7)	2.3 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
7	2.4 (2.3-2.6)	2.3 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
8	2.4 (2.2-2.5)	2.2 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
9	2.4 (2.2-2.5)	2.2 (2.1-2.4)	0.01 (0.00-0.01)	0.01 (0.00-0.02)
10	2.4 (2.2-2.5)	2.2 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
11	2.4 (2.2-2.5)	2.3 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
12	2.4 (2.3-2.6)	2.3 (2.1-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)

CI: confidence interval

eTable2-8

### Type 1 diabetes

Month(s) before diagnosis	Outpatient Monthly visit (95% CI)		Inpatient Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	3.4 (3.2-3.6)	2.4 (2.4-2.5)	0.03 (0.01-0.04)	0.01 (0.01-0.02)
2	3.0 (2.9-3.1)	2.4 (2.4-2.5)	0.02 (0.01-0.03)	0.01 (0.01-0.01)
3	2.8 (2.7-2.8)	2.4 (2.4-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
4	2.6 (2.5-2.7)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
5	2.5 (2.4-2.6)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
6	2.4 (2.4-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
7	2.4 (2.3-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
8	2.4 (2.3-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
9	2.4 (2.4-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
10	2.4 (2.4-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
11	2.5 (2.4-2.5)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
12	2.5 (2.4-2.6)	2.4 (2.4-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)

CI: confidence interval

eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)  
eTable2-9

Myasthenia gravis				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.0 (4.3-5.8)	2.3 (2.0-2.6)	0.04 (-0.03-0.11)	0.01 (0.00-0.01)
2	4.0 (3.6-4.4)	2.3 (2.1-2.5)	0.04 (0.00-0.09)	0.01 (0.00-0.01)
3	3.4 (3.1-3.7)	2.3 (2.1-2.5)	0.04 (0.01-0.08)	0.01 (0.00-0.02)
4	3.0 (2.8-3.3)	2.4 (2.2-2.5)	0.04 (0.01-0.07)	0.01 (0.00-0.02)
5	2.8 (2.6-3.1)	2.4 (2.2-2.6)	0.04 (0.01-0.07)	0.01 (0.00-0.02)
6	2.7 (2.4-2.9)	2.4 (2.2-2.6)	0.03 (0.01-0.06)	0.01 (0.00-0.02)
7	2.6 (2.4-2.9)	2.4 (2.2-2.6)	0.03 (0.00-0.05)	0.01 (0.00-0.02)
8	2.6 (2.4-2.8)	2.4 (2.2-2.6)	0.02 (0.00-0.04)	0.01 (0.00-0.02)
9	2.6 (2.4-2.9)	2.4 (2.2-2.6)	0.02 (0.00-0.03)	0.01 (0.00-0.02)
10	2.7 (2.4-2.9)	2.4 (2.2-2.6)	0.01 (0.00-0.03)	0.01 (0.00-0.02)
11	2.7 (2.5-3.0)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
12	2.8 (2.5-3.0)	2.4 (2.2-2.6)	0.01 (0.00-0.02)	0.01 (0.00-0.02)

CI: confidence interval

eTable2-10

Systemic lupus erythematosus				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	7.2 (6.7-7.7)	2.2 (2.1-2.4)	0.56 (0.41-0.71)	0.01 (0.00-0.02)
2	5.3 (5.1-5.6)	2.3 (2.2-2.4)	0.26 (0.16-0.36)	0.01 (0.00-0.01)
3	4.3 (4.0-4.5)	2.4 (2.3-2.5)	0.12 (0.06-0.17)	0.01 (0.00-0.01)
4	3.6 (3.4-3.8)	2.4 (2.3-2.5)	0.06 (0.03-0.09)	0.01 (0.00-0.01)
5	3.1 (3.0-3.3)	2.4 (2.3-2.6)	0.03 (0.01-0.05)	0.01 (0.00-0.01)
6	2.9 (2.7-3.0)	2.5 (2.3-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)
7	2.7 (2.6-2.8)	2.5 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
8	2.6 (2.5-2.7)	2.5 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
9	2.6 (2.4-2.7)	2.4 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
10	2.5 (2.4-2.7)	2.4 (2.3-2.6)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
11	2.6 (2.4-2.7)	2.4 (2.3-2.5)	0.02 (0.01-0.03)	0.01 (0.00-0.01)
12	2.6 (2.4-2.7)	2.4 (2.3-2.5)	0.02 (0.01-0.03)	0.01 (0.00-0.01)

CI: confidence interval

**eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)**  
eTable2-11

### Rheumatoid arthritis

Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.3 (4.9-5.8)	2.4 (2.2-2.6)	0.48 (0.31-0.64)	0.01 (0.00-0.01)
2	4.6 (4.3-4.9)	2.4 (2.3-2.6)	0.23 (0.14-0.33)	0.01 (0.00-0.01)
3	4.0 (3.8-4.3)	2.4 (2.3-2.5)	0.12 (0.06-0.17)	0.01 (0.00-0.01)
4	3.7 (3.5-3.9)	2.4 (2.3-2.6)	0.06 (0.03-0.10)	0.01 (0.00-0.01)
5	3.4 (3.2-3.6)	2.4 (2.3-2.6)	0.04 (0.02-0.06)	0.01 (0.00-0.01)
6	3.2 (3.0-3.4)	2.4 (2.3-2.6)	0.03 (0.01-0.05)	0.01 (0.00-0.01)
7	3.0 (2.9-3.2)	2.5 (2.3-2.6)	0.03 (0.01-0.04)	0.01 (0.00-0.01)
8	3.0 (2.8-3.1)	2.5 (2.3-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)
9	2.9 (2.7-3.0)	2.5 (2.4-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)
10	2.8 (2.7-3.0)	2.5 (2.4-2.6)	0.02 (0.01-0.04)	0.01 (0.00-0.01)
11	2.8 (2.7-3.0)	2.5 (2.4-2.6)	0.03 (0.01-0.04)	0.01 (0.00-0.01)
12	2.8 (2.7-2.9)	2.5 (2.4-2.6)	0.03 (0.01-0.04)	0.01 (0.00-0.01)

CI: confidence interval

eTable2-12

### Severe burns

Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	2.4 (2.1-2.7)	2.5 (2.3-2.7)	0.00 (0.00-0.00)	0.01 (0.00-0.02)
2	2.4 (2.2-2.5)	2.5 (2.4-2.6)	0.00 (0.00-0.01)	0.01 (0.00-0.01)
3	2.3 (2.2-2.5)	2.5 (2.4-2.6)	0.00 (0.00-0.01)	0.01 (0.00-0.01)
4	2.3 (2.2-2.4)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
5	2.3 (2.2-2.4)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
6	2.3 (2.2-2.4)	2.5 (2.3-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
7	2.3 (2.2-2.4)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
8	2.3 (2.2-2.4)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
9	2.3 (2.2-2.5)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
10	2.3 (2.2-2.5)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
11	2.4 (2.2-2.5)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
12	2.4 (2.3-2.5)	2.5 (2.4-2.6)	0.01 (0.00-0.01)	0.01 (0.00-0.01)

CI: confidence interval

eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)  
eTable2-13

Severe injuries				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	2.3 (2.2-2.5)	2.3 (2.2-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.02)
2	2.3 (2.2-2.5)	2.3 (2.3-2.4)	0.01 (0.00-0.02)	0.01 (0.00-0.01)
3	2.3 (2.3-2.4)	2.4 (2.3-2.4)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
4	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
5	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
6	2.4 (2.3-2.5)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
7	2.4 (2.3-2.5)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
8	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
9	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
10	2.4 (2.3-2.4)	2.4 (2.3-2.5)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
11	2.4 (2.3-2.4)	2.4 (2.3-2.4)	0.01 (0.00-0.01)	0.01 (0.01-0.01)
12	2.4 (2.3-2.4)	2.4 (2.3-2.4)	0.01 (0.00-0.01)	0.01 (0.01-0.01)

CI: confidence interval

eTable2-14

All 7 cancers				
Month(s) before diagnosis	Outpatient		Inpatient	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	5.8 (5.6-6.0)	2.4 (2.3-2.5)	0.33 (0.27-0.39)	0.01 (0.01-0.02)
2	4.4 (4.3-4.5)	2.4 (2.4-2.5)	0.14 (0.12-0.17)	0.01 (0.01-0.01)
3	3.5 (3.5-3.6)	2.4 (2.4-2.5)	0.06 (0.05-0.08)	0.01 (0.01-0.01)
4	3.0 (2.9-3.1)	2.4 (2.4-2.4)	0.03 (0.03-0.04)	0.01 (0.01-0.01)
5	2.7 (2.6-2.7)	2.4 (2.4-2.4)	0.02 (0.02-0.03)	0.01 (0.01-0.01)
6	2.5 (2.5-2.6)	2.4 (2.4-2.4)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
7	2.4 (2.4-2.4)	2.4 (2.4-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
8	2.4 (2.3-2.4)	2.4 (2.4-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
9	2.3 (2.3-2.4)	2.4 (2.3-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
10	2.4 (2.3-2.4)	2.4 (2.3-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
11	2.4 (2.4-2.4)	2.4 (2.3-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
12	2.4 (2.4-2.5)	2.4 (2.3-2.4)	0.01 (0.01-0.01)	0.01 (0.01-0.01)

CI: confidence interval

**eTable2: Numbers and confidence intervals corresponding to Figure 1 (Continued)**  
eTable2-15

<b>All 4 immune diseases</b>				
<b>Month(s) before diagnosis</b>	<b>Outpatient</b>		<b>Inpatient</b>	
	Monthly visit (95% CI)		Monthly visit (95% CI)	
	Cases	Controls	Cases	Controls
1	4.7 (4.5-4.8)	2.4 (2.3-2.4)	0.24 (0.19-0.30)	0.01 (0.01-0.01)
2	3.9 (3.8-4.0)	2.4 (2.3-2.4)	0.11 (0.09-0.13)	0.01 (0.01-0.01)
3	3.4 (3.3-3.4)	2.4 (2.4-2.4)	0.05 (0.04-0.06)	0.01 (0.01-0.01)
4	3.0 (3.0-3.1)	2.4 (2.4-2.5)	0.03 (0.02-0.04)	0.01 (0.01-0.01)
5	2.8 (2.7-2.9)	2.4 (2.4-2.5)	0.02 (0.02-0.02)	0.01 (0.01-0.01)
6	2.7 (2.6-2.7)	2.4 (2.4-2.5)	0.02 (0.01-0.02)	0.01 (0.01-0.01)
7	2.6 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
8	2.5 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
9	2.5 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
10	2.5 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
11	2.5 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
12	2.5 (2.5-2.6)	2.4 (2.4-2.5)	0.01 (0.01-0.01)	0.01 (0.01-0.01)

CI: confidence interval

eTable3: Numbers and confidence intervals corresponding to Figure 2

		Odds Ratios (95% confidence intervals)		Odds Ratios (95% confidence intervals)	
Malignant neoplasm of bone and articular cartilage	RESP	0.88 (0.76-1.02)	Type 1 diabetes	RESP	1.14 (1.10-1.19)
	IM	1.11 (0.71-1.71)		IM	1.18 (1.04-1.34)
	GI	1.26 (0.88-1.80)		GI	1.97 (1.79-2.17)
	URO	--		URO	2.47 (2.01-3.03)
	INJ	6.62 (4.89-8.97)		INJ	1.27 (1.09-1.48)
Soft tissue cancers	NEURO	3.01 (0.92-9.84)	Myasthenia gravis	NEURO	1.36 (1.09-1.69)
	RESP	1.14 (0.96-1.35)		RESP	1.04 (0.90-1.19)
	IM	0.84 (0.53-1.32)		IM	0.79 (0.51-1.21)
	GI	1.92 (1.33-2.75)		GI	1.15 (0.81-1.63)
	URO	2.49 (0.78-7.89)		URO	--
Ovarian cancer	INJ	4.05 (2.62-6.27)	Systemic lupus erythematosus	INJ	0.89 (0.52-1.50)
	NEURO	0.77 (0.24-2.48)		NEURO	2.63 (1.25-5.54)
	RESP	1.04 (0.85-1.28)		RESP	1.63 (1.52-1.75)
	IM	1.25 (0.67-2.31)		IM	1.74 (1.50-2.02)
	GI	3.31 (2.24-4.91)		GI	1.80 (1.57-2.08)
Brain tumour	URO	3.50 (2.00-6.10)	Rheumatoid arthritis	URO	2.65 (2.18-3.23)
	INJ	--		INJ	1.95 (1.62-2.35)
	NEURO	2.80 (0.82-9.52)		NEURO	1.85 (1.30-2.64)
	RESP	1.30 (1.22-1.39)		RESP	1.20 (1.10-1.31)
	IM	1.29 (1.08-1.54)		IM	1.61 (1.28-2.02)
Lymphomas	GI	2.29 (2.01-2.61)		GI	1.67 (1.35-2.08)
	URO	2.27 (1.49-3.48)		URO	2.91 (1.56-5.43)
	INJ	1.63 (1.32-2.01)		INJ	2.12 (1.79-2.50)
	NEURO	3.42 (2.86-4.09)		NEURO	1.74 (1.05-2.89)
	RESP	1.44 (1.31-1.58)			
Acute lymphoid leukaemia	IM	1.37 (1.09-1.72)			
	GI	1.45 (1.15-1.82)			
	URO	1.55 (0.82-2.94)			
	INJ	2.86 (2.15-3.81)			
	NEURO	1.11 (0.53-2.31)			
Acute myeloid leukaemia	RESP	1.42 (1.35-1.49)			
	IM	1.29 (1.09-1.53)			
	GI	1.60 (1.41-1.82)			
	URO	2.48 (1.65-3.73)			
	INJ	2.39 (2.00-2.87)			
	NEURO	1.01 (0.73-1.38)			
	RESP	1.77 (1.61-1.96)			
	IM	1.10 (0.80-1.52)			
	GI	1.48 (1.15-1.90)			
	URO	2.54 (1.13-5.71)			
	INJ	2.53 (1.74-3.67)			
	NEURO	1.24 (0.54-2.87)			