

## Letter to the Editor

**Prevalence of indolent systemic mastocytosis in a Dutch region**

*To the Editor:*

Mastocytosis is a rare disease. Remarkably, incidence or prevalence data of mastocytosis have never been collected. We aimed to generate prevalence data on the indolent and the related smoldering form of systemic mastocytosis (SM) in the adult population of the Groningen region in The Netherlands.

In cutaneous mastocytosis, the accumulation of abnormal mast cells is limited to the skin. In SM, abnormal mast cells are present in at least 1 extracutaneous tissue site. Manifestations in adults can vary from characteristic symptoms such as typical skin lesions (urticaria pigmentosa [UP]) and flushing to less characteristic symptoms such as osteoporosis, diarrhea, and anaphylaxis, especially after an insect sting. Nearly all adult patients have indolent systemic mastocytosis (ISM) or smoldering systemic mastocytosis (SSM) with a (near) normal life expectancy.<sup>1</sup> Only a few patients harbor one of the more aggressive forms with severe symptoms and a reduced survival.

Different sources were used to collect prevalence data. First, all consecutive adult patients from the University Medical Center Groningen (UMCG), a national referral center for mastocytosis and a Center of Excellence in the European Competence Network of Mastocytosis,<sup>2</sup> with a confirmed or suspected diagnosis of UP or SM were registered from 1981. Second, the UMCG laboratory database was searched for potential patients, because the UMCG laboratory has a regional function in the determination of serum tryptase from 2001 and in the detection of the D816V mutation of the *C-KIT* proto-oncogene in bone marrow and blood samples from 2007. Third, the registries of the departments of Pathology and Dermatology of the other hospital (Martini Hospital) in the city of Groningen were used. These registries contain data on all histological diagnoses and all patients with the diagnosis of UP from 2000.

The diagnosis of ISM and SSM was established by using the criteria of the World Health Organization Classification of Mastocytosis.<sup>3</sup> If bone marrow data were unavailable or insufficient, ISM was presumed if UP was present combined with serum tryptase level of 20 µg/L or more. This assumption is based on the fact that all UMCG patients with this combination had SM (n = 120). High risk of ISM was defined as (a) the combination of UP and serum tryptase level between 10 and 20 µg/L (ISM was diagnosed in 37 of 39 UMCG patients with this combination) or (b) the combination of clinical suspicion, serum tryptase level of more than 10 µg/L, and elevated histamine metabolites in urine, if UP was absent.<sup>4</sup> The diagnosis of UP was made clinically by experienced dermatologists and confirmed by histological examination of a lesional biopsy.

To calculate the prevalence, the home address on January 1, 2011, for each living patient aged 15 years or more was verified during the regular visit at our outpatient clinic in 2011, by confirmation in the (nonmobile) phone book, or by phoning patients or their general physicians. Being a national referral center and a Center of Excellence of the European Competence Network of Mastocytosis may induce bias in prevalence data. To prevent bias as much as possible, we only included patients living in the Groningen region. The UMCG and the Martini Hospital in

the city of Groningen are encircled by hospitals in 5 neighboring cities (Delfzijl, Winschoten, Assen, Drachten, and Dokkum). Assuming that the majority of patients are referred to the hospital at the shortest distance, the border of the Groningen region was defined by the middle of the distances between the city center of Groningen and those of the surrounding 5 cities. These borders of the Groningen region and those of the postal code zones within this region are depicted in Fig E1 (in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Data on the age distribution of the general population in the different postal code zones on January 1, 2011, were found at the site of Statistics Netherlands.<sup>5</sup> The Medical Ethical Review Board of the UMCG declared that the study has been done in accordance with regulations of the review board for publication of patient data.

A total of 42 patients were identified as living in the Groningen region. Of these patients, 34 originated from a total of 263 patients in the UMCG mastocytosis registry. In addition, 3 from the UMCG laboratory database and 5 patients from the registries of the Martini Hospital were identified.

Of the total of 42 patients, 30 (71%) had ISM, 1 (2%) SSM, 2 (5%) presumed ISM, and 9 (22%) a high risk for ISM (5 with UP). Suspicion to start ISM diagnostics was based on UP (n = 31), anaphylaxis after being stung by wasp or bee (n = 4), osteoporosis (n = 5), anaphylaxis by unknown reason (n = 1), and urticaria (n = 1). Sixteen (38%) were men, and the median age was 54.7 (range, 18.6-74.5) years. The prevalence of ISM and SSM, presumed ISM, and high ISM risk combined (shortly ISM prevalence) in the Groningen region population aged 15 years or more was 13.0 per 100,000 inhabitants on January 1, 2011. Fig 1 shows the ISM prevalence in the different age categories and in the total population aged 15 years or more (Fig 1, A) and the year ranges in which the diagnosis was established (Fig 1, B). The population size in the Groningen region did not substantially change in the last years (about 11% increase between 1998 and 2011).

Fig 1, A, demonstrates that ISM prevalence increases with age, but remarkably no cases were found in the oldest age category (≥75 years). Nowadays, most cases are diagnosed in middle age, missing the elderly. The lack of awareness of attending physicians in the past (Fig 1, B) might be a logical explanation for the absence of cases in the oldest age category, because ISM is a chronic disease and complete remissions are very rare in adults, if occurring at all. In addition, the World Health Organization criteria for diagnosing mastocytosis including new laboratory techniques were developed only in 2001.<sup>6</sup>

Fig 1, B, shows a steep increase in the number of ISM patients from 1998 to 2010. This increase is very likely to be the result of an increase in the experience of the mastocytosis team and the continuing educational activities of the team to allergologists, dermatologists, hematologists, internists, and general practitioners during these years. It underlines the relevant role of centers of excellence and reference centers of the European Competence Network of Mastocytosis in detecting and treating patients with mastocytosis.<sup>2</sup>

With a prevalence of at least 13.0 per 100,000 inhabitants and with an average of 1940 patients aged 15 years or more per full-time working general practitioner,<sup>7</sup> 1 out of 4 Dutch first-line physicians will be responsible for an adult patient with ISM, assuming that the prevalence in the Groningen region is

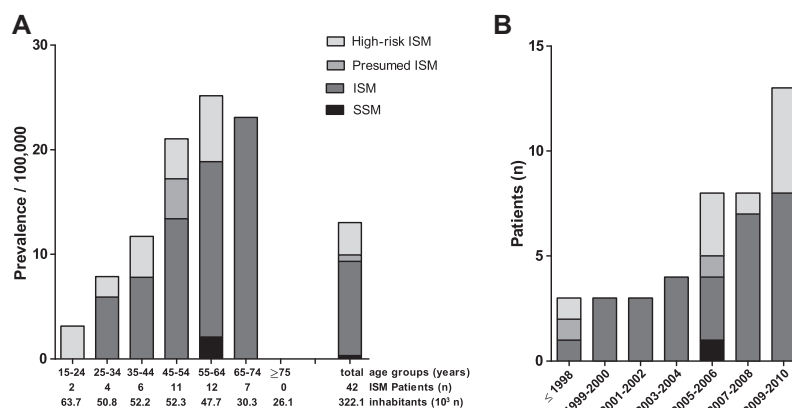


**FIG 1.** The prevalence of ISM, presumed ISM, high risk on ISM, and SSM in the different age categories and in the total population aged 15 years or more (A) and the years in which the diagnosis has been established (B).

representative of the whole Dutch nation. The actual prevalence might be higher because ISM diagnosis may easily be missed as symptoms can be subtle or absent, together with the lack of awareness of this disease.

In summary, the ISM prevalence in the adult population in the Groningen region, The Netherlands, is at least 13 cases per 100,000 inhabitants.

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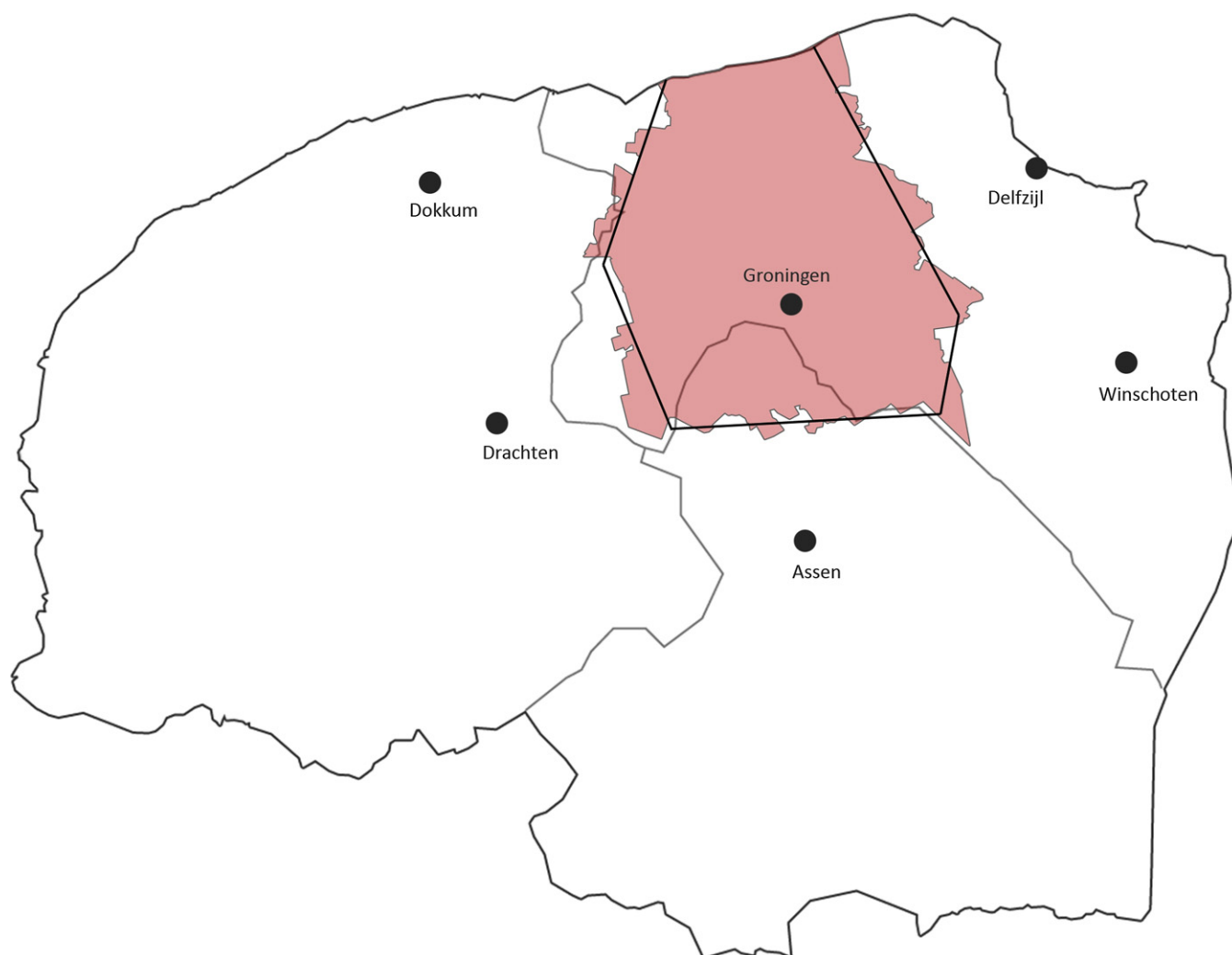


**FIG E1.** The border of the Groningen region as defined by the middle of the distances between the city center of Groningen and those of the surrounding 5 cities (*straight black lines*) and that of the postal code zones within this region (*red-colored area*).