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Research paper

# Incidence of myelodysplastic syndromes in Finland 1997–2016

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## SUMMARY

Myelodysplastic syndromes (MDS) are a diverse group of clonal hematopoietic stem cell diseases that may progress to acute myeloid leukemia. Here, we present incidence of myelodysplastic syndromes based on a nationwide, registry-based study. A total of 1906 MDS cases were reported to the Finnish Cancer Registry during 1997–2016. We analysed the age-standardized incidence rates using the new European standard population, incidence trend and changes in trend by sex, age group and calendar year using Poisson regression and joinpoint regression. The average age-standardized incidence rate was 3.92 per 100,000 person-years. The incidence of MDS increased in a linear-quadratic fashion across 10-year age groups and was higher among men (5.43 versus 3.14 per 100,000). The incidence trend increased during the first 15 years followed by a decline towards the end of the study period. A similar trend was found in subgroups by sex and age. Our results show a similar or slightly higher MDS incidence in Finland as in other Western countries, with an increasing trend, but some decrease in the end. The increasing incidence may reflect improved reporting and coding, or there could be a genuine increase in MDS over time.

## 1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell (HSC) diseases, typically characterized by dysplasia of the myeloid cell lines, inefficient haematopoiesis and peripheral cytopenia in one or more cell lines. MDS are regarded as preleukemic states, which may, in one third of the patients [1], progress to acute myeloid leukemia [1–5]. The main risk factors for MDS are old age, male gender, previous chemotherapy or radiotherapy, family history of hematopoietic neoplasms, and exposure to chemical carcinogens such as benzene and formaldehyde [1,3–5]. The diagnosis of MDS is based on blood and bone marrow examinations. The prognosis of the disease depends on the proportion of blasts in bone marrow, severity of cytopenia and somatic gene or karyotype abnormalities [1].

Miscellaneous terms including refractory anemia and preleukemia have been used in the past to describe bone marrow failure with anemia as predominant manifestation, which is typical for MDS [6]. The French-American-British classification provided the first consistent framework in 1982 [7]. The World Health Organization (WHO) developed the subsequent classifications published in 2001, 2008 and 2016

[4,8]. MDS became reportable to cancer registries in 2001, after being classified as a malign condition in the Tenth Revision of the International Classification of Diseases (ICD-10) and in the Third Revision of the ICD Oncology (ICD-O-3) [9]. Research on occurrence of MDS is complicated by changes over time in diagnostic activities and criteria as well as classification practices at cancer registries [10]. This has also led to paucity of studies on MDS incidence.

Previous studies of the incidence of MDS, in the Netherlands, Germany, Switzerland and the USA, have reported overall age-standardized incidence rate (ASIR) ranging 2.5–3.4 per 100,000 person-years [11–14]. A large study based on 44 different cancer registries estimated that the ASIR of MDS in Europe years 2000–2002 was 1.24 per 100,000 person-years [15]. According to an Oceanian study, the ASIR of MDS was 3.2 in Australia and 3.7 in New Zealand [16]. The U.S. Surveillance Epidemiology and End Results cancer registration program of the National Cancer Institute only started to cover MDS in 2001 [17].

Several studies have found higher incidence of MDS among men than women and major increases with age [4,11–14,16,18]. According to studies in Caucasian populations, the incidence rate ratio (IRR) for men relative to women ranges from 1.7 to 2.0. The increase in incidence rates

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with age is also steeper among men than women [11–14]. In a Swiss study, the incidence of MDS increased exponentially after 60 years of age [11]. In a US study, the incidence rate of MDS was triple among 70–74-year-olds compared to the age group of 60–64 years, and almost sevenfold at age 80–84 years [14]. In the Netherlands, the incidence rate in the age group of 70–79 years was about double and after age 80 years about fourfold compared to ages 60–69 years [12].

Some studies also show variation in MDS incidence rates by ethnic group [14,19,20]. Ma et al. reported highest incidence rate of MDS among white people (3.5/100,000) and lowest among Native Americans and Alaskans (1.3/100,000), with rates in African Americans in between (3.0/100,000) [14]. A ten years younger median age at MDS diagnosis was reported in Japan, China and Thailand compared to the Western countries [19–21].

In general, epidemiological studies on MDS remain scarce, likely at least partly due to repeated revisions of classification and diagnostic criteria posing challenges for compiling large study materials. We are not aware of any previous studies of the incidence of MDS in Finland or in the Nordic countries, even if these countries have a long tradition of high-quality cancer registration.

Our objective was to examine the incidence of myelodysplastic syndromes in Finland during 1997–2016, with evaluation of incidence trends and any changes during the study period. In addition, the incidence of MDS is analysed in subgroups defined by age, sex and time period.

## 2. Materials and methods

Information on numbers of MDS cases per year by sex and age group during 1997–2016 was obtained from the NORDCAN database, which provides cancer statistics for the Nordic countries. NORDCAN follows international database rules, which improves the comparability between countries [22,23].

We collected data from the NORDCAN database also for the years 1992–1996, but excluded as low rates suggested incomplete coverage. With the exclusion of the early years, the ICD-10-classification covered the whole study period reducing changes in coding.

Ten-year age groups were used, though the youngest age group was 0–39 years and the oldest 80 years and older. Data on Finnish population size by year, sex and ten-year age group were obtained from the Statistics Finland population database. Ten-year age groups were chosen instead of five-year age groups for simplicity and clarity in the analyses and illustrations, and also to ensure data protection and privacy, since some strata with five-year age groups had < 5 cases. For the same reasons, five-year calendar periods were used instead of single years.

We calculated the crude and age-standardized incidence rates for MDS for the whole study population, for men and women separately, for ten-year age groups and in five-year calendar periods. For age-standardization, the European standard population (ESP 2013) was used as the reference [24]. In Table 1, we also report age-standardized rates calculated with the Finnish population (in addition to ESP). Trend over time was evaluated using Poisson regression, with numbers of cases as the outcome and annual population size as the offset term. Differences in incidence trends between subgroups were evaluated using interaction terms, with improvement in goodness of fit of nested models as the criterion (based on likelihood ratio tests). Departure from linearity in incidence trends was examined using a squared term of the calendar-year and age. Finally, a joinpoint regression analysis was performed to further assess potential changes in incidence trend, beyond the average annual change in incidence. Such change points could occur due to e.g., revision in classification or coding practices.

The Poisson regression analyses were conducted using Stata (version 16). The joinpoint analysis was performed with JoinPoint regression software [25].

The data are entirely registry-based, with no individual identifiers. No evaluation by an ethical committee is required for such studies

**Table 1**

Incidence rates of myelodysplastic syndromes in Finland by age, sex and calendar period during 1997–2016.

	N	%	Incidence rate per 100,000 person-years		
			Crude	Age-standardized (Finland)	Age-standardized (Europe)
<b>Overall</b>	1906	100.0	1.80	5.28	3.92
<b>Sex</b>					
Male	931	48.8	1.80	7.06	5.43
Female	975	51.2	1.80	4.34	3.14
<b>Age</b>					
< 40 years	23	1.2	0.04	–	–
40–49 years	34	1.8	0.23	–	0.23
50–59 years	73	3.8	0.48	–	0.48
60–69 years	213	11.2	1.77	–	1.79
70–79 years	576	30.2	7.28	–	7.20
80 + years	987	51.8	21.85	–	22.57
<b>Year</b>					
1997–2001	269	14.1	1.04	3.54	2.61
2002–2006	383	20.1	1.46	4.53	3.45
2007–2011	670	35.2	2.50	6.94	5.26
2012–2016	584	30.6	2.14	5.51	4.01

according to the Finnish regulation, nor permission from registry holder, or consent. The data contain no small enough frequencies to jeopardize privacy or allow identification of individual patients.

## 3. Results

In total, 1906 MDS cases were registered in Finland 1997–2016, 975 (51.2%) of which were in women and 931 (48.8%) among men. The ASIR (Europe) for the whole study population was 3.92 per 100,000 person-years (Table 1).

The incidence rates were significantly higher among men compared to women and the difference was more prominent in older age groups (Fig. 1). The ASIR (Europe) for men was 5.43 and for women 3.14 per 100,000 person-years (Table 1). The IRR (women to men) was 0.61 with the 95% confidence interval, CI 0.56–0.67.

The incidence of MDS was very low at ages before 60 years, but after that the incidence rates sharply increased (Fig. 1). On average, the incidence increased four-fold per each decade of age. The ASIR (Europe) was 1.79 per 100,000 person-years in the age group of 60–69 years, 7.20 for the age group of 70–79 years and 22.57 for the ages 80 + years (Table 1). The increase in incidence with age was greater among men.

The incidence of myelodysplastic syndromes increased during the study period (Fig. 2), with the highest incidence during the period of 2007–2011. As the low ASIR toward the end of the study period may represent incomplete or delayed reporting, we also analysed the data excluding the year 2016, but this did not appreciably affect the age-standardized incidence (ASIR (Europe) 4.01 versus 3.92 per 100,000).

In a linear regression analysis, the incidence of MDS increased during the study period on average 0.18 cases per 100,000 per year (0.24 cases per 100,000 per year when 2016 was excluded). The increase over time was not linear, as evidenced by a significant improvement in model fit by adding a squared year term ( $p < 0.001$ ) in the Poisson regression. In addition, different trends in subgroups of sex and age were found ( $p$  for interaction  $< 0.001$  for both). The increase in incidence was steeper among men: the average yearly increase was 0.29 cases per 100,000 for men and 0.10 for women. For the age groups of 60–69, 70–79 and over 80 years, the incidence increased on average 0.05, 0.23 and 0.68 cases per 100,000 per year, respectively.

Joinpoint regression analysis was performed to analyse changes in incidence trends. In the entire study population, one joinpoint was found, in 2011. Segmental annual percentage changes (APC) for the

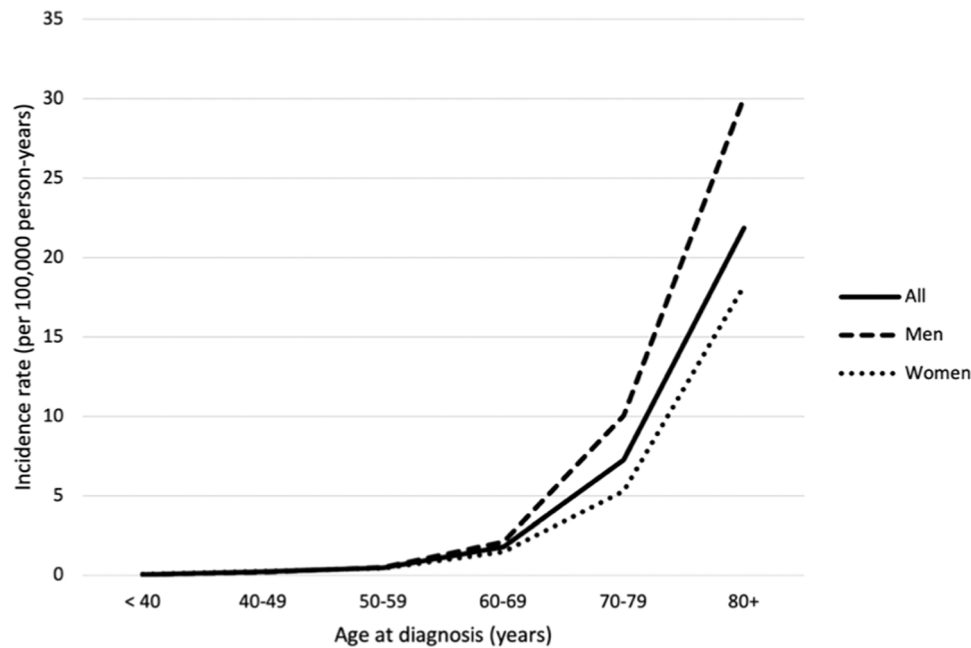


Fig. 1. Incidence rates of MDS per 100,000 person-years by 10-year age group for men, women and overall.

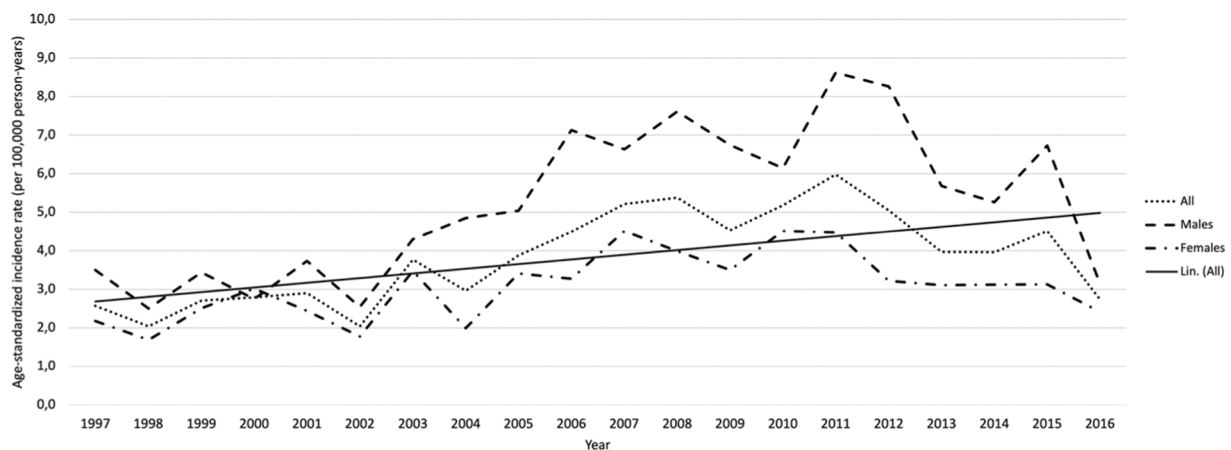


Fig. 2. Age-standardized incidence of MDS in Finland 1997–2016 by sex and in the entire population.

ASIR (Finland) were 7.0 for the period 1997–2011 (95% CI 4.5–9.5) and –11.2 in 2011–2016 (95% CI –19.1 to –2.5). Similarly, as a single joinpoint was detected among women, with segmental APC's of 6.1 (1997–2010) (95% CI 3.1–9.2) and –8.2 (2010–2016) (95% CI –15.1 to –0.9) and in men, with segmental APC's of 8.2 for 1997–2011 (95% CI 4.5–12.0) and –12.0 (95% CI –22.6 to –0.8). Joinpoint regression analyses for the age groups of 60–69 years, 70–79 years and 80 + years showed similar results in all three groups, with one joinpoint in 2011 and patterns comparable to that in the entire material, i.e., an increase throughout the first 15 years with a declining trend in the end.

A secondary Poisson regression analysis based on the Finnish cancer registry data with ICD-10 diagnosis code D46 showed no clear changes during 2010–2018 among men or women (IRR 0.99, 95% CI 0.96–1.02 for change in incidence per year in men and 0.97, 95% CI 0.93–1.00 for women).

#### 4. Discussion

The age-standardized incidence of MDS increased in Finland during the study period. Besides a real increase, this could reflect more

complete reporting to the cancer registry, as well as improved diagnosis and coding. However, some decrease was found toward the end of the study period. The incidence was higher among men than women, especially in older age groups.

The average ASIR (Europe) in our study for 1997–2016 was 3.92 per 100,000 person years, which is slightly higher compared with the other European MDS studies using a similar reference population. Incidence was closest to the rates reported in other European countries in the late 1990 s. However, most previous European MDS studies have used the old European standard population.

In a German study based on the Düsseldorf MDS registry, an incidence of 2.51 per 100,000 was reported for 1986–2001 [13]. A study based on the Netherlands Cancer Registry showed incidence rates 2.3–2.8 per 100,000 during 2001–2010 [12]. A Swiss study covering a more recent study period found incidence rates 2.45–2.53 per 100,000 for 2001–2012 based on the Swiss Cantonal Cancer Registries [11]. The HAEMACARE project studied the epidemiology of hematological malignancies in Europe years 2000–2002 using data from 44 cancer registries and reported an ASIR of 1.24 per 100,000 person-years for MDS in Europe, which is markedly lower than incidence in Finland. After Britain

and Ireland, MDS incidence was highest in the Northern Europe [15].

Additionally, a population-based study in the US using the 2000 US Standard Population reported an incidence of 3.4 per 100,000 in 2001–2003 based on the Surveillance, Epidemiology and End Results (SEER) and the North American Association of Central Cancer Registries (NAACCR) data [14]. Furthermore, the age-standardized incidence rates in Australia (3.2 per 100,000 person-years) and New Zealand (3.7 per 100,000 person-years), estimated based on the New Zealand Cancer Registry and Australian Cancer Incidence and Mortality data years 2005–2007 using the world standard population, were comparable to our results [16]. In Asia, the incidence rates of MDS are substantially below those in Finland and other Western countries. In China, an ASIR of 1.14 per 100,000 person-years was reported for 2004–2007 using the Chinese standard population of the year 1982 [21].

The ASIR (Europe) among Finnish men and women were 5.43 and 3.14 per 100,000 person-years. These are in the higher range of results reported in previous from Europe, Australia and the US. They have shown incidence rates for men ranging from 3.34 to 4.50 per 100,000 person-years and for women from 1.80 to 3.30 per 100,000 person-years [11–14,16]. In New Zealand, incidence rates are exceptionally high for men (5.4 per 100,000 person-years), though comparable to our results [16]. In China and Japan, in contrast, the incidence rates are remarkably low: in China approximately 1.5 per 100,000 for both men and women, and in Japan 1.6 for men and 0.8 for women [18,21].

Male predominance in MDS incidence has been reported in several previous studies. The male-female standardized IRR in our study was 1.73, which is somewhat lower than those reported from most of the other countries. IRR was 1.8 in Germany, 1.9 in Switzerland, the Netherlands and Australia, 2.0 in Japan and 2.1 in New Zealand [11–13, 16,18]. In the USA, IRR (1.67) was comparable to our study [14]. China was the only country with a slight female predominance (IRR 0.96 for men) [21].

In our study, there were more cases among women than men (51.2% vs. 48.8%), but nevertheless the age-standardized incidence rates (European and Finnish) were higher among men compared to women. That is due to the population structure, with a female predominance, which is more prominent in the older age groups, where also the incidence of MDS is the highest. Population and disease cases at younger age are weighted more heavily in the age-standardized rates, and therefore they are higher in men than women, unlike crude rates.

Our data showed a strong increase in incidence rates with age, mainly after 60 years, which is comparable to earlier studies [11–14,16, 18]. The incidence increased four-fold per decade of age. Also, a Swiss study has characterized the increase after 60 years of age as exponential [11]. We also found that the increase is steeper among men than women, which has also been found in previous studies [11–14,16,18].

We found an increasing trend in incidence until the five-year period 2007–2011, followed by a slight decrease for 2012–2016. Modest increases in incidence have been reported also from the USA, Switzerland and the Netherlands. In the USA, the incidence rate rose from 3.28 to 3.56 per 100,000 person-years during 2001–2003 [14]. In Switzerland, the ASIR was 2.45 during 2001–2007 and 2.53 in 2008–2012, with a slight increase among men and decrease among women [11]. Lastly, in the Netherlands, the crude incidence rate increased from 2.3 per 100,000 in 2001–2005 to 2.8 per 100,000 in 2006–2010 [12].

The joinpoint analysis showed two segments with different trends during the study period. The increasing incidence in the early study period is likely to be at least partly due to the improving knowledge and changing classification of the disease. In general, changes in awareness of the disease, classification and criteria, improved reporting to cancer registries, and increased frequency of radiotherapy and chemotherapy for other cancers may contribute to the increasing incidence trend of MDS. In the interpretation of the results, the average annual change estimated with Poisson regression assumes a constant rate of change over the study period, while the joinpoint analysis is aimed at detecting changes in trend. Hence, their assumptions are incompatible, and we are

more confident in the results of the Poisson analysis using the overall data.

MDS onset is insidious and presents frequently with a prolonged cytopenia that could be due to a variety of other conditions or agents such as malignant, immunological or metabolic diseases, deficiencies or toxic exposures. Differential diagnosis can involve aplastic anemia, pernicious anemia, chronic myeloid leukemia, congenital syndromes, as well as reactive bone marrow changes. Bone marrow examinations required to demonstrate morphological, genetic and karyotypic aberrations typical for MDS and ascertaining the diagnosis have probably become more frequent in elderly patients with peripheral blood abnormalities and it is likely that fewer cases are therefore missed during more recent periods than earlier. Also, routine peripheral blood counts in asymptomatic patients may lead to incidental diagnosis of early MDS.

Classification updates developed by the WHO were implemented in Finland in a timely manner, first in major hospitals treating especially younger patients and more serious cases. Accordingly, the new diagnostic methods at time, such as genetic testing, were likely applied with some delay in the oldest age groups and among patients with good prognosis. However, it is difficult to assess whether this would bias the rates in the oldest age groups, because the revisions have not always consistently broadened or restricted the inclusion of patients under the MDS category and hence adoption of revised classifications is unlikely to have systematically increased or decreased the numbers of cases.

The reason for decreasing incidence trend during the recent years remains unclear, though likely involves underreporting related to introduction of new medical information systems and increased patient load. The observed changes in time do not coincide with the introduction of revised disease classifications, nor with the transfer from ICD-O2 to ICD-O-3, as the joinpoints in the incidence curves occurred around 2010–2011.

A study assessing the coverage and accuracy of myeloproliferative and myelodysplastic neoplasms in the Finnish Cancer Registry (FCR) years 2007–2013 by comparing the FCR data to hospital discharge data reported a low coverage for MDS of only 37.5% [26]. The ICD-O-3 was introduced in 2007, improving the registration of MDS in FCR. Earlier, MDS cases were not registered if MDS was the only diagnosis. However, to improve the registry data, in 2015 FCR screened the deleted reports and imported missing cases of MDS and myeloproliferative neoplasms to the database for all years, also before 2007. These changes should not affect the comparisons by age or sex.

This is the first population-based epidemiological study providing information about the incidence of MDS in Finland. The strengths of our study include the long study period spanning two decades up to 2016, a large study population representing the whole of Finland, and detailed analyses of incidence trend of MDS. Our study also had some limitations. Information on subtypes of myelodysplastic syndromes was not available and therefore we were unable to assess incidence by specific diagnosis. Therapy-related MDS could not have been ruled out, since we were unable to collect data of first primary malignancies only. In addition, the data for the year 2016 seemed incomplete, though exclusion of data for 2016 did not appreciably affect the results. The inaccuracy and complex nature of registration of MDS are likely to add uncertainty in the results.

In conclusion, the incidence of MDS in the Finnish population was similar to or slightly above other Western countries. There was a marked increase during the study period, though the incidence trend changed over time with a possible decrease in the latest years. We were unable to determine to what extent the increasing incidence is due to improved coverage and coding of the disease at the cancer registry or whether there is also a true increase in the risk of MDS.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence



the work reported in this paper.

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Suvi Kontro performed the research. Anssi Auvinen designed the study and conceived the analysis plan. Suvi Kontro, Anssi Auvinen and Jani Raitanen analysed the data. Suvi Kontro wrote the first version of the manuscript. Anssi Auvinen, Jani Raitanen and Kimmo Porkka critically revised the paper. No fundings were allocated to this research. This paper is Suvi Kontro's thesis for the licenciate degree program in medicine.

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