

Prevalence of smoldering Waldenström macroglobulinemia: the nationwide iStopMM screening study

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Background: Smoldering Waldenström macroglobulinemia (SWM) is an asymptomatic precursor to Waldenström macroglobulinemia (WM), defined by IgM monoclonal protein and $\geq 10\%$ bone marrow lymphoplasmacytic infiltration without WM-defining features. SWM is preceded by IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) and carries a substantially higher risk of progression to symptomatic WM than IgM-MGUS. Because distinguishing SWM from IgM-MGUS requires bone marrow biopsy, the population prevalence of SWM has not previously been established. Existing epidemiological data are limited to cancer registries and hospital-based cohorts, which cannot capture the true population burden of asymptomatic precursor disease.

Objective: To estimate the age- and sex-specific prevalence of SWM in the general population and to describe the clinical and laboratory characteristics of SWM cases.

Methods: The iStopMM study (Iceland Screens, Treats, or Prevents Multiple Myeloma; ClinicalTrials.gov NCT03327597) is a prospective, nationwide, population-based screening study in Iceland. All residents aged ≥ 40 ($n=148,704$) were invited to participate; 75,094 individuals were screened for monoclonal gammopathy by serum protein electrophoresis and free light chain analysis. Participants with a monoclonal protein detected on screening, regardless of isotype, were randomized to one of three follow-up arms. This analysis is restricted to participants with IgM or multiple isotype monoclonal gammopathy. In arms 2 and 3, bone marrow sampling was performed systematically per protocol. Point prevalence of SWM was estimated by age group and sex from the proportion of IgM or multiple isotype participants in arms 2 and 3 diagnosed with SWM by bone marrow biopsy, and were extrapolated to the full iStopMM cohort. Direct standardization was used to estimate the prevalence in the 2018 Icelandic population. Continuous age-prevalence relationships were modeled using logistic regression with restricted cubic splines.

Findings: Fifty-one individuals were diagnosed with SWM, 47 of whom were enrolled in arms 2 and 3 (fig. 1). The overall crude prevalence of SWM was 0.13% (95% CI 0.10 - 0.15%) and the age- and sex-standardized prevalence was 0.12% (95% CI 0.10 - 0.15%). The

prevalence increased markedly with age, from 0.05% in both sexes aged 50-59 to 0.55% (95% CI 0.28 - 0.81%) in females aged > 80 and 0.3% (95% CI 0.10 - 0.50%) in males aged > 80; no cases were identified below age 50 (fig. 2). There was a statistically significant increase in prevalence by age ($p < 0.001$), but no statistically significant difference by sex ($p = 0.52$). The median age among all SWM cases was 73 years, with a near-equal sex distribution (51% male, 49% female). According to the IPSSWM, 35% were low risk, 61% intermediate risk, and 3.2% high risk.

Interpretation: The prevalence of SWM in the Icelandic population is 0.12% among individuals aged 40 years or older, rising substantially with age. Screen-detected SWM is characterized by predominantly low- and intermediate-risk disease and near-equal sex distribution, contrasting with the male predominance previously reported in clinically ascertained cohorts. This is, to our knowledge, the first population-based estimate of SWM prevalence, providing an epidemiological foundation for future studies of natural history and for the ongoing debate over monitoring intensity and early intervention in WM precursor conditions.

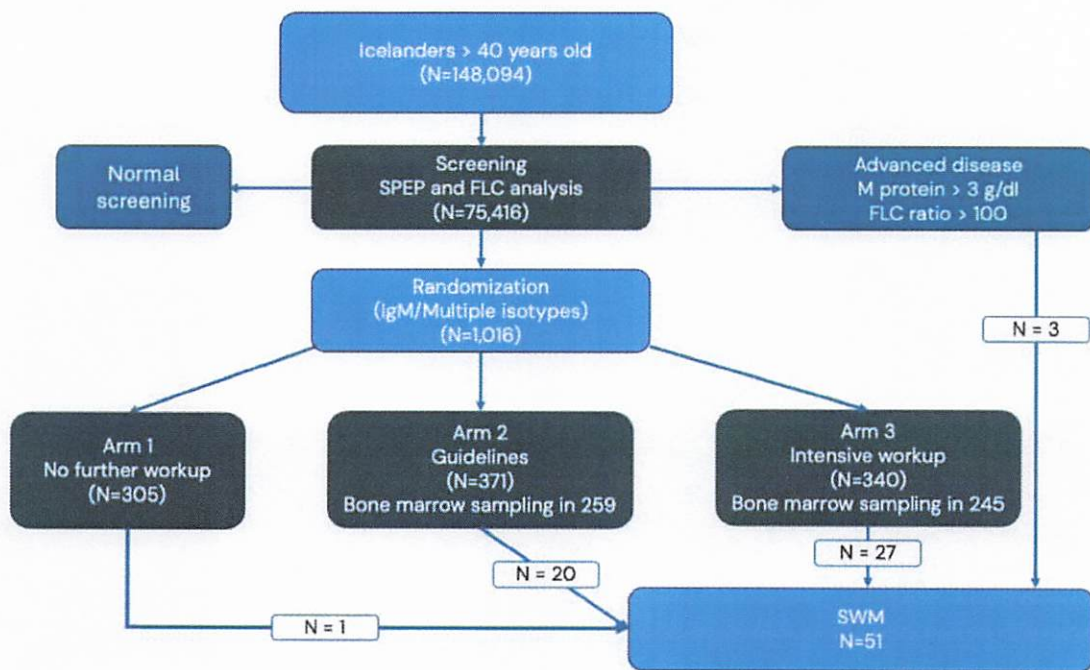


Figure 1: Flowchart of the study population.

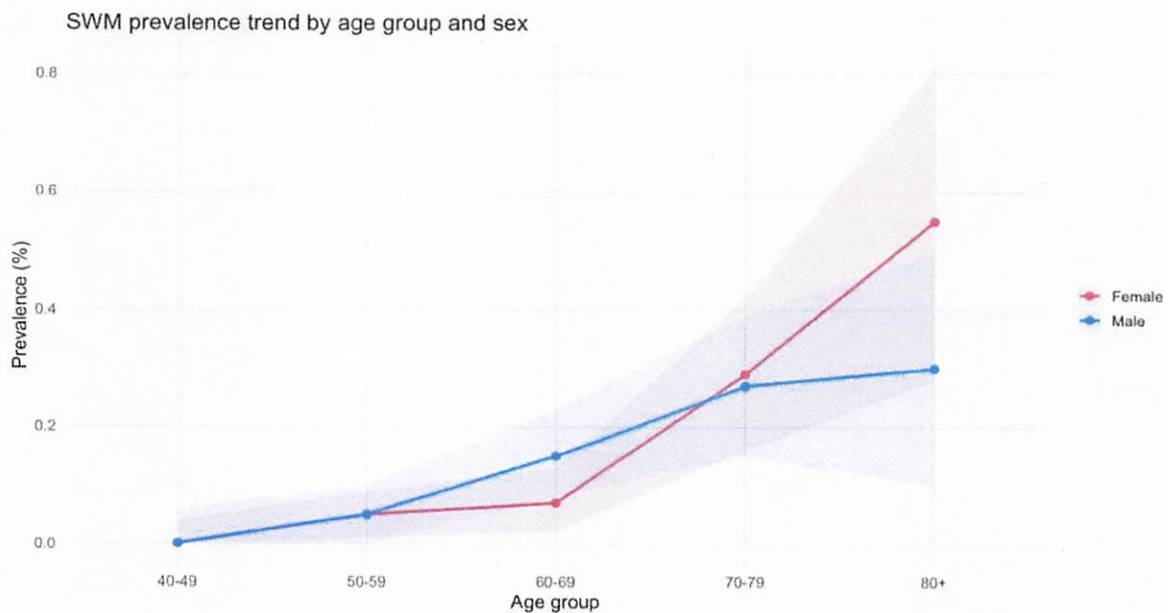


Figure 2: Estimated prevalence of SWM by age group and sex among all participants of the iStopMM study.

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