Comment on: Prevalence, incidence and geographical distribution of familial Mediterranean fever in Turkey

Sir,

I read with interest the paper by Satış *et al*. on the prevalence, incidence and geographical distribution of familial Mediterranean fever (FMF) in Turkey (1). This nationwide study using electronic health records represents an important contribution. However, there are a number of issues in the methods and results that should be addressed.

First, there is a numerical inconsistency in the prevalence estimates. In a population of 82,003,882 residents in Turkey in 2018, the authors initially identify 199,685 individuals with FMF. After excluding all patients aged ≥50 years who had both colchicine treatment and an ICD-10 code for gout, they report that 160,897 FMF patients remained. Simple division (160,897 / 82,003,882) yields an overall prevalence of 19.6 per 10,000, not 139 per 10,000 as stated in the text. The published numbers therefore do not reproduce the reported prevalence, suggesting an error either in the calculation or in the figures presented (perhaps showing per 10,000 instead of per 100,000?).

Second, the age-specific prevalences in Figures 2A and 2B (1) are incompatible with an overall prevalence of 139 per 10,000. None of the age groups exceed approximately 30-35 per 10,000 and most lie around 15-20 per 10,000. With this pattern, it is mathematically impossible to obtain a mean of 139 per 10,000 across the population.

Third, the reported prevalence of 139 per 10,000 (1.39%; roughly 1 in 70 individuals) is implausibly high in comparison with other much more commonly encountered inflammatory diseases such as rheumatoid arthritis or ankylosing spondylitis (both found 0.49% in Turkey) (2, 3). It is also far above the range reported in previous population-based FMF surveys from Turkey, which have generally found prevalences between about 27 and 820 per 100,000 depending on region, ethnicity and age group (Table I) (4-9). It must also be mentioned that FMF prevalence among ethnic Armenians, a minority group, in Istanbul reached 760-870 per 100,000, substantially higher than general population estimates, with 36% carrying MEFV mutations *versus* 20% in non-Armenians (4). The prevalence reported in the adult population of Tokat (a city in Northern Anatolia) (820/100,000) was close to that found in this ethnic minority (5). Other surveys reported considerably lower rates suggesting a non-homogenous distribution of FMF in Turkey.

Fourth, there are concerns about case definition. The authors state that they screened individuals with ICD-10 codes "E85, E85.0, E85.1, E85.2, E85.3, E85.4, E85.8, M85.9". These codes largely represent various hereditary and non-hereditary amyloidosis syndromes; none is specific for FMF. This strategy may risk including amyloidosis patients without FMF as cases, yet the justification for using these codes as proxies for FMF is not discussed in the Methods. The study's reliance on ICD-10 codes without clinical validation or sensitivity analysis is particularly problematic given documented diagnostic challenges in FMF (10). In addition, M85.9 denotes "disorder of bone density and structure, unspecified" and appears to be a typographical error that should be corrected in both the text and figure legends.

Fifth, the exclusion of all patients aged ≥50 years who have both colchicine treatment and gout in order to "avoid misdiagnosing gout as FMF" could be troublesome. Such an exclusion disproportionately censors older adults and alters the apparent age distribution of FMF as seen in the sharp non-biological decline in Figures 2A and 2B (1).

Finally, elements of transparent reporting are missing. The authors state that Figure 2B (1) is "corrected according to the number of individuals applying to the health care facilities" but do not specify the data source. Geographical distribution of FMF is mentioned in the title but no information regarding this has been given. They also note that the highest prevalence was observed in the provinces of Ardahan, Bayburt and Sivas, yet they do not provide the actual regional prevalence values. Moreover, none of the incidence and prevalence estimates are accompanied by confidence intervals, contrary to modern epidemiological reporting standards.

I believe that a formal correction and a clear explanation of how the prevalence estimates were derived are necessary before these data can be used to inform the true burden of FMF in Turkey.

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Competing interests: none declared.

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Table I. Familial Mediterranean fever prevalence studies previously done in Turkey.

Reference	Studies by city / region or ethnicity	Age range (year) of the screened population	Patients with FMF n (male/ female)	Population screened, n	FMF prevalence per 100,000 (95% confidence interval)
Kısacık *et al*.	Tokat/Northern Anatolia	>18	9 (3/6)	1.095	820 (290–1350)
Onen *et al*.	Sivas/ Central Anatolia	0–70	10 (8/2)	3948	250 (90–410)
Dinc *et al*.	Nationwide	18–22 (among men)	50 (50/0)	45.745	110 (80–140)
Ozen *et al*.	Ankara / Central Anatolia	≤16 (paediatric population)	33 (not specified)	35.284	93 (60–120)
Cobankara *et al*.	Denizli / Western Anatolia	7–17	2 (2/0)	7.389	27 (-10–70)
Seyahi *et al*.	Armenian minority living in Istanbul	>25 (parents only) Part.1	12 (6/6)	1380	870 (380-1360)
		0-70 (parents and siblings) Part 2.	34 (18/16)	4462	760 (510-1002)