

Demographic characteristics of patients with extrapulmonary tuberculosis in Germany

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## **Abstract**

**Setting:** Germany, 1996-2000.

**Objective:** To determine demographics of patients with extrapulmonary tuberculosis in Germany

**Design:** Analysis of data on 26,302 tuberculosis cases from a national survey

**Results:** The crude proportion of patients with extrapulmonary manifestations among tuberculosis patients was 21.6%. Extrapulmonary tuberculosis was most likely among females, children below the age of 15 years, and among persons originating from Africa and Asia. Females tended to be more likely to have any form of extrapulmonary tuberculosis than males except pleural tuberculosis. The strength of this association was strongest in the age band 25 to 65 and less pronounced amongst the oldest patients. Children were particularly prone to develop lymphatic and meningeal tuberculosis, while the likelihood for genitourinary tuberculosis increased with increasing age. Asian and African patients were generally more likely than persons from other areas to have lymphatic, osteoarticular, meningeal, and miliary tuberculosis.

**Conclusion:** This analysis shows important differences by age, sex, and origin in the likelihood that a tuberculosis patient presents with extrapulmonary tuberculosis. Since the relative contribution of the foreign-born to tuberculosis in low-prevalence countries is rising, extrapulmonary tuberculosis must be taken into account more often in the differential diagnostic work-up of these patients, particularly among those originating from Asia and Africa.

In contrast to reports from other industrialized countries [1, 2], no change in the proportion of extrapulmonary tuberculosis has been reported in Germany over the recent past [3]. In addition to the impact of infection with the human immunodeficiency virus (HIV) and demographic changes in the tuberculosis population other factors may affect the proportion of tuberculosis patients with extrapulmonary manifestations.

In Germany, little is known about HIV infection among tuberculosis patients as this investigation is neither routinely done nor are such results notifiable [4, 5]. Furthermore, tuberculosis continued to decline at the time the most increase in acquired immunodeficiency syndrome (AIDS) was noted [6]. An ongoing study by the German Central Committee against Tuberculosis shows that the prevalence of HIV infection continues to play a minor role among tuberculosis patients, irrespective of their provenance (German Central Committee against Tuberculosis, unpublished data).

This study describes some key demographic and clinical characteristics of patients with extrapulmonary tuberculosis in Germany.

## Methods

In the five-year period from 1996 to 2000 a total of 52,455 tuberculosis cases were notified in Germany, a country with approximately 82 million inhabitants. This corresponded to an average annual notification rate of 12.8 per 100,000 population. To obtain more detailed information on tuberculosis patients living in Germany, a large survey was conducted for a study period encompassing the years 1996 through 2000 [7]. In the 16 states that constitute Germany, there are 467 public health service offices, one at each district level, that were asked to participate in the study. Of these, 257 (55%) participated continuously. A questionnaire was completed by these offices providing information on demographic characteristics of patients (age, sex, residence, citizenship, country of birth, and time of immigration to Germany for foreigners), disease-specific characteristics (site and form of disease and bacteriologic findings, drug susceptibility test results), and socio-economic factors (source of income, housing characteristics). The information was centrally collated and computerized. The cases participating public health service offices contributed to the study constitute approximately 50 per cent of all cases reported in Germany. A comparison of patient characteristics between the study population and the total patient population suggested close comparability in all characteristics examined (age distribution, sex, proportion foreign-born).

Until the end of the year 2000, all notified tuberculosis cases in Germany had been classified as respiratory (including pulmonary, intrathoracic lymphatic, and pleural) tuberculosis. In this study, in addition to the “respiratory classification system”, the more detailed classification into pulmonary and extrapulmonary tuberculosis (including intrathoracic lymphatic and pleural tuberculosis) was applied according to the European consensus on surveillance of tuberculosis [8]. This allowed flexibility to reclassify tuberculosis according to the older system, yet at the same time comparison with others, such as the classification scheme of the United States Centers for Disease Control and Prevention and the American Thoracic Society [9]. Since 2001, the new classification system alone is in vigor.

The data were electronically captured with Epi Info (Version 6.04d, US Centers for Disease Control and Prevention) and analyzed using EpiData Analysis (Version 2.0, EpiData Association, Denmark, [www.epidata.dk](http://www.epidata.dk), 2007) and Stata version 9.2 (StataCorp LP, College Station, Texas, USA, 2007). Having an extrapulmonary tuberculosis was the main outcome

for these analyses and the proportion of extrapulmonary tuberculosis was calculated by dividing the number of patients with extrapulmonary tuberculosis by all patients (in respective age-groups or groups of origin). Multivariable logistic regression models with extrapulmonary tuberculosis as the outcome variable were subsequently fitted. The models included indicator variables for being female, for belonging to the specified age groups, and the regions of origin. The models included appropriately constructed effect modification terms to assess effect modifications between sex and age groups and age groups and region of origin. Models with and without effect modification terms were compared by likelihood ratio tests and substantial effect modifications were found. Because of the complexity of communicating results from models including several effect modification terms, we decided to present results from stratified analyses by presenting the relative odds for extrapulmonary tuberculosis being female compared to male patients, stratified by age group and country / area of origin with 95% confidence intervals obtained from stratified logistic regression models.

## Results

In the study period, a total of 26,333 cases were reported in the study area. Of these, 13 had unknown age, 15 unknown sex, and three both unknown sex and age. These 31 cases were excluded from analysis and thus 26,302 were included in all analyses.

Of the 20,627 cases of pulmonary tuberculosis, 73.4% had a bacteriological confirmation of *Mycobacterium tuberculosis* complex by culture, as compared to 59.3% of the 5,675 extrapulmonary cases (table 1). Among extrapulmonary cases, bacteriological confirmation was most frequent for genitourinary tuberculosis (77.9%) and lowest among cases with intrathoracic lymphatic tuberculosis (38.8%).

The crude prevalence of extrapulmonary tuberculosis as the major disease site was 21.6% (5,675 cases) (table 2). The proportion of extrapulmonary sites differed considerably by the three characteristics that were examined: females had almost twice as frequently extrapulmonary tuberculosis than males, children below the age of 15 years had by far the highest proportion among all age groups, and persons originating from Asia or Africa had extrapulmonary tuberculosis in excess of 30 per cent.

Of all patients with extrapulmonary tuberculosis, 58.7% were born in Germany, 32.1% per cent were patients from countries with a higher risk of extrapulmonary tuberculosis than the former (i.e., from other Western European countries, Turkey, Africa, Asia, and other / unknown), and 9.2% from countries with a lower risk (Eastern Europe, Newly Independent States of the former Soviet Union (NIS) (table 2). Of the 9,646 foreign-born patients, 53.5% (5,160) had information on month and year of entry into Germany. Among these, tuberculosis was diagnosed in 89.3% (4,607) within the first 12 years after arrival. Considering the latter 4,607 cases only, in 44.7% (1,565) of the 3,502 with pulmonary tuberculosis the diagnosis was made within the first year, while the respective proportion among the 1,105 cases with extrapulmonary tuberculosis was 28.1% (310). The annual frequency dropped sharply in subsequent years for both pulmonary and extrapulmonary tuberculosis (figure 1) with a similar shape of decline, but more protracted for extrapulmonary than pulmonary tuberculosis.

In all countries, and in virtually every age group, females were more likely to have extrapulmonary tuberculosis than males (figure 2). Up to age 24 years, the differences were often not statistically significant, but tended to be so among those older when the number of patients was large and the confidence intervals thus narrower. There was also a tendency that

the odds of being female decreased again among the oldest patients, with the notable exceptions of patients from western European countries other than Germany and patients from Asia.

The eight most frequent extrapulmonary sites were stratified by age and sex and the odds of being a female with extrapulmonary tuberculosis determined (figure 3). Except for pleural tuberculosis (no overall increased odds) and miliary tuberculosis, the age-specific odds appeared to be bimodal with a nadir in the age groups between 15 and 34 years of age and a peak in those aged 45 to 64 years.

The proportion of foreign-born tuberculosis cases in Germany rose from 31.4 per cent in 1996 to 37.4 per cent in the year 2000. But the growth of the fraction born in Turkey, Africa, and Asia in this period from 15.5 percent to 18.5 per cent was evidently too small to impact on the overall proportion of extrapulmonary tuberculosis, which remained stable at 21.6 per cent on average (data not shown).

## Discussion

The data presented here were collected in a national survey eliciting all health departments to participate in the study. As participation in this survey was voluntary, it was not possible to ensure representative sampling. Nevertheless, more than half of the health departments participated continuously over a period of five years, and a comparison of certain characteristics of participating with available characteristics of all patients reported in this period in Germany lends some credibility that the participating centers catered for a similar clientele as the rest of the country.

Tuberculosis among immigrants tends to cluster frequently in the initial period following arrival [11, 12]. What has been shown for the United Kingdom and the United States [12] was similarly apparent in this study. This contrasts findings from Denmark, where the risk of tuberculosis continued to emerge at a more similar magnitude over a prolonged period of time subsequent to immigration [13]. While screening of immigrants may partially explain the identification of prevalent cases at the time of entry, an important contributor for the early occurrence is seemingly the role of recently acquired infection in the country of origin [11] and the declining risk of progression with time elapsed since infection [14]. In Denmark, transmission within the foreign population after arrival was estimated to account for one quarter of cases among Somali residents, yet the majority of cases was still attributed to acquisition of *M. tuberculosis* infection before immigration. The observation of a delayed presentation of extrapulmonary compared to pulmonary tuberculosis relative to time of immigration may be partially explained by screening at entry which prominently targets pulmonary tuberculosis. Furthermore, many forms of extrapulmonary tuberculosis are manifestations emerging on average after a longer interval following acquisition of infection than pulmonary tuberculosis [15].

The emergence of tuberculosis among immigrants can be largely attributed to an infection that has been acquired in their country of origin [16]. Nevertheless, data from the Netherlands [17] and Denmark [18] clearly show that transmission of *M. tuberculosis* among immigrants also takes place following arrival, and that this may account in certain settings for a considerable proportion of cases [18].

Differences in the likelihood for extrapulmonary tuberculosis have been observed in various studies among tuberculosis patients by demographic characteristics. However, the reasons remain by and large elusive. On the individual level, there are indications for subtle anomalies in innate immune function [19, 20]. However, it is difficult to reconcile how such

differences might apply to larger population groups, and find different expressions for various sites of disease.

It is established [15] that certain forms of tuberculosis have a predilection for young ages, such as intrathoracic lymphatic tuberculosis [21, 22], while genitourinary tuberculosis is rarely found in children [1, 23, 2]. Such differences may partially be explained by maturation factors and development of the cellular immune system [24]. Furthermore, the manifestation of tuberculosis is intrinsically linked to time elapsed since infection was acquired, making it difficult to separate the modifying effects of age and recency of infection. Common wisdom holds for instance that pleural tuberculosis is intrinsically linked to recent acquisition of infection. However, this notion is seemingly substantiated in some [25], but not confirmed in other studies [26] using molecular characterization of strains.

As observed in other studies [1], female tuberculosis patients were, with the exception of pleural tuberculosis, considerably likelier to present with an extrapulmonary manifestation than male patients. The reasons for this preponderance are not clearly known. The increased likelihood of women with tuberculosis to present with an extrapulmonary disease manifestation was particularly pronounced among those aged 45 to 64 years. An explanation for this finding remains elusive, but suggests that perhaps endocrine factors play a role.

The differences in the proportion of extrapulmonary tuberculosis by area of origin are remarkable. Patients from Africa and Asia were generally far more likely to present with extrapulmonary tuberculosis than tuberculosis patients from Germany. The recent demonstration that a loss-of-function polymorphism in the *P2X<sub>7</sub>* gene increases susceptibility to extrapulmonary tuberculosis in patients from South-East Asia suggests that genetic factors may explain some of these differences [27]. The critical role of vitamin D in macrophage function is well known and it has long been postulated, particularly in the United Kingdom [28], that the high rates of tuberculosis in general seen among immigrants from countries where sunlight is plentiful might in part be explained by the relative deficiency of the vitamin upon arrival in countries less favored by sunshine. It appears, nevertheless, that much of this is conjecture, and other, epidemiological reasons can provide a much more parsimonious answer. In particular, the vitamin D hypothesis probably fails to explain organ-specific predilections and differences between persons from a different area of origin.

The contrary to what was seen among patients from Africa and Asia was seen in patients from countries of the former Soviet Union and Eastern Europe who showed a lower risk for extrapulmonary tuberculosis. In this context, it might be noted that for instance in Estonia, pulmonary tuberculosis markedly increased subsequent to independence while there was little change in the incidence of extrapulmonary tuberculosis, and not an increase in those forms considered to have a long latency period [29].

The increased likelihood for extrapulmonary tuberculosis among patients from Africa in particular may be partially explained by the expected higher prevalence of HIV infection amongst this patient group compared to patients from Germany. Over the past 20 years, HIV infection has been identified to cause more frequently extrapulmonary disease manifestations [30] and was indeed once a defining definition for AIDS. In The Netherlands, a similar proportion of extrapulmonary tuberculosis among patients from Africa was observed as in this study, but also a much higher proportion among persons with a Dutch nationality than was found here among those born in Germany [31]. That the higher prevalence of HIV cannot fully explain observed differences is evidenced with the example of tuberculosis patients from Asia. This group of patients is expected to have on average a lower frequency of HIV infection. Yet, the preponderance of Asians for lymphatic tuberculosis is well known [32, 33]. Indeed, in a study from New York City on extrapulmonary tuberculosis among

immigrants, HIV infection among patients with extrapulmonary tuberculosis was less frequent than among those with pulmonary tuberculosis [34]. This study also showed that among all foreign-born, those from the former Soviet Union had the lowest frequency of extrapulmonary tuberculosis, comparable to those born in the United States.

Smoking appears to increase the risk of pulmonary, but not of extrapulmonary tuberculosis [35], and would thus increase the odds of extrapulmonary compared to pulmonary tuberculosis in population groups with a lower prevalence of smoking. From the data collected in this study, it cannot be evaluated if smoking had an impact on the observed differences.

Immigration is increasing in many European countries and the composition of immigrants is changing its pattern. It is thus not unexpected to find the epidemiology of tuberculosis in the immigrant's place of origin increasingly reflected in tuberculosis disease manifestation in their newly adapted residence.

Over one fifth of tuberculosis patients in Germany presents now with an extrapulmonary disease manifestation, and this proportion is considerably increased among female patients, children, and among some foreign-born patients such as Asians and Africans. This calls for considerable diagnostic acumen on the part of physicians treating such patients.

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Table 1. Frequency of bacteriological confirmation by culture of *Mycobacterium tuberculosis* complex among reported tuberculosis cases, by site of disease, Germany, 1996-2000

Disease site	Culture-confirmed		No culture confirmation	Total
	Number	Per cent		
Total	18,501	70.3	7,801	26,302
Pulmonary	15,134	73.4	5,493	20,627
Extrapulmonary	3,367	59.3	2,308	5,675
Lymphatic, peripheral	859	51.0	826	1,685
Lymphatic, intrathoracic	223	38.8	352	575
Pleural	579	55.2	470	1,049
Genitourinary	746	77.9	212	958
Osteoarticular	326	71.3	131	457
Miliary	126	68.5	58	184
Meningeal	91	68.4	42	133
Peritoneal	65	56.0	51	116
Cutaneous	70	60.9	45	115
Other	282	70.0	121	403



Table 2. Extrapulmonary manifestation of tuberculosis, by sex, age group, and area of origin, Germany, 1996-2000.

Characteristic	Extrathoracic lymphatic	Intrathoracic lymphatic	Pleural	Genito-urinary	Osteo-articular	Miliary	Meningeal	Peritoneal	Cutaneous	Other	Total EPTB	Total TB	% EPTB of TB
Total	1,685	575	1,049	958	457	184	133	116	115	403	5,675	26,302	21.6
Per cent of extrapulmonary	29.7	10.1	18.5	16.9	8.1	3.2	2.3	2.0	2.0	7.1	100.0	--	--
Sex													
Female	1,080	321	342	469	222	93	69	67	65	208	2,936	9,806	29.9
Male	605	254	707	489	235	91	64	49	50	195	2,739	16,496	16.6
Age (years)													
00-14	97	196	25	1	14	5	12	6	5	12	373	1,066	35.0
15-24	163	69	132	14	40	7	12	16	4	29	486	2,332	20.8
25-34	372	76	203	60	77	24	24	29	6	64	935	4,269	21.9
35-44	262	63	171	104	40	14	19	17	15	44	749	4,355	17.2
45-54	147	38	106	186	45	19	20	16	8	42	627	3,380	18.6
55-64	185	43	126	238	80	28	21	10	29	59	819	3,844	21.3
65 and older	459	90	286	355	161	87	25	22	48	153	1,686	7,056	23.9
Country of birth													
Germany	747	285	679	758	252	139	75	40	91	263	3,329	16,656	20.0
Western Europe	39	12	21	22	9	2	0	0	1	8	114	490	23.3
Eastern Europe	115	46	88	48	29	12	12	7	4	21	382	2,534	15.1
NIS	24	11	35	37	17	0	6	3	2	6	141	1,385	10.2
Turkey	190	66	70	41	23	2	9	15	2	26	444	1,547	28.7
Africa	142	47	48	14	45	8	12	19	5	28	368	1,140	32.3
Asia	370	95	83	26	67	17	17	27	9	47	758	1,947	38.9
Other / unknown	58	13	25	12	15	4	2	5	1	4	139	603	23.1

TB: Tuberculosis

EPTB: Extrapulmonary tuberculosis

NIS: Newly Independent States for the former Soviet Union

Figure 1. Interval between arrival in Germany and diagnosis of tuberculosis among the foreign born, by year of arrival, among cases developing within the first 12 years after arrival, Germany, 1996-2000.

Figure 2. Female-to-male odds ratio of having extrapulmonary tuberculosis, by age group and country / area of origin. To ensure comparability, the scale of the ordinate was constrained to always show the same range, resulting in truncation in some figures of the point estimate (hollow circles) and / or the 95% confidence interval (vertical lines). The horizontal dashed line represents unity.

Figure 3. Age-specific female-to-male odds ratios of extrapulmonary compared to pulmonary tuberculosis, by site of extrapulmonary disease, Germany, 1996-2000

Figure 1.

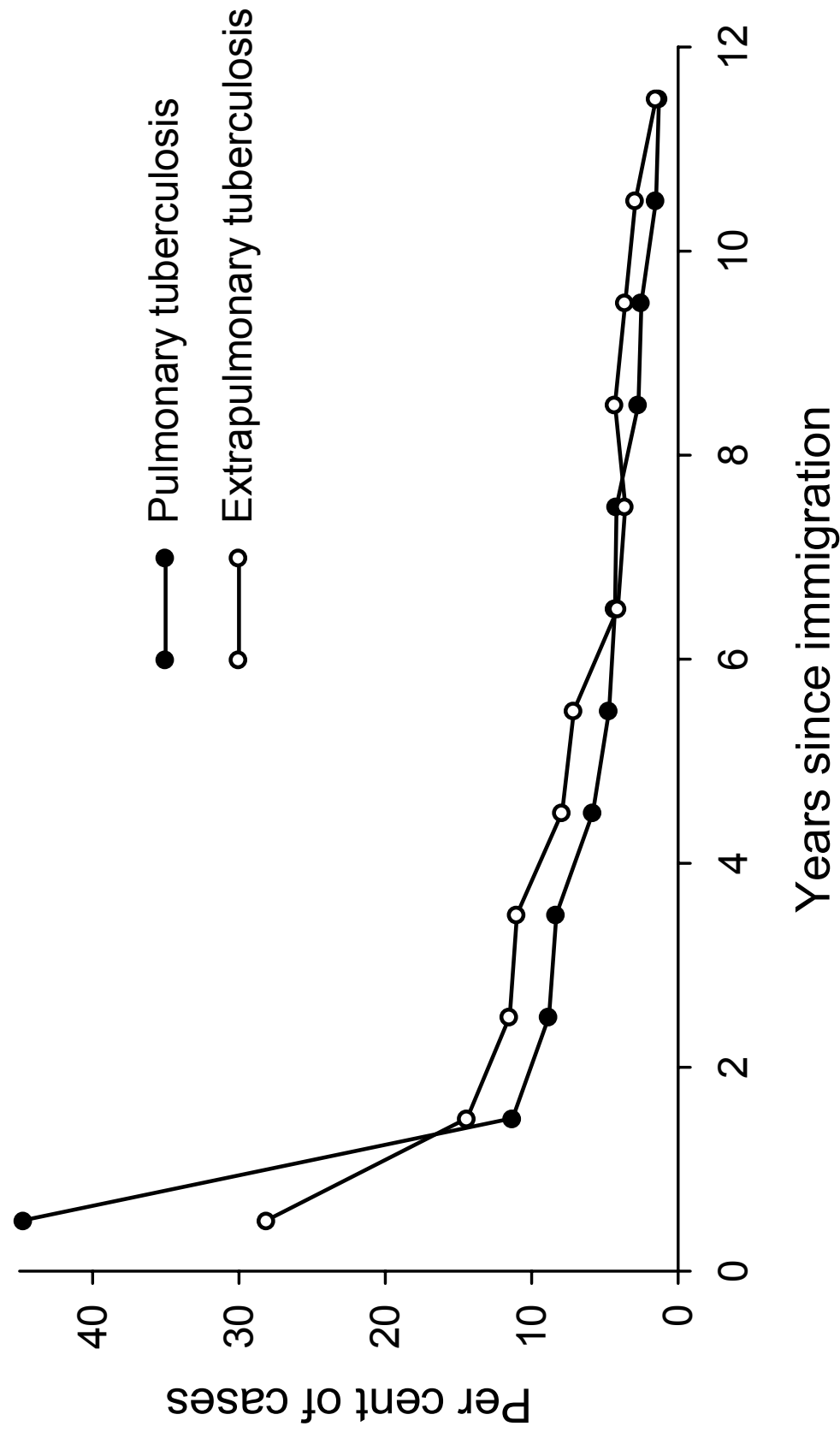


Figure 2.

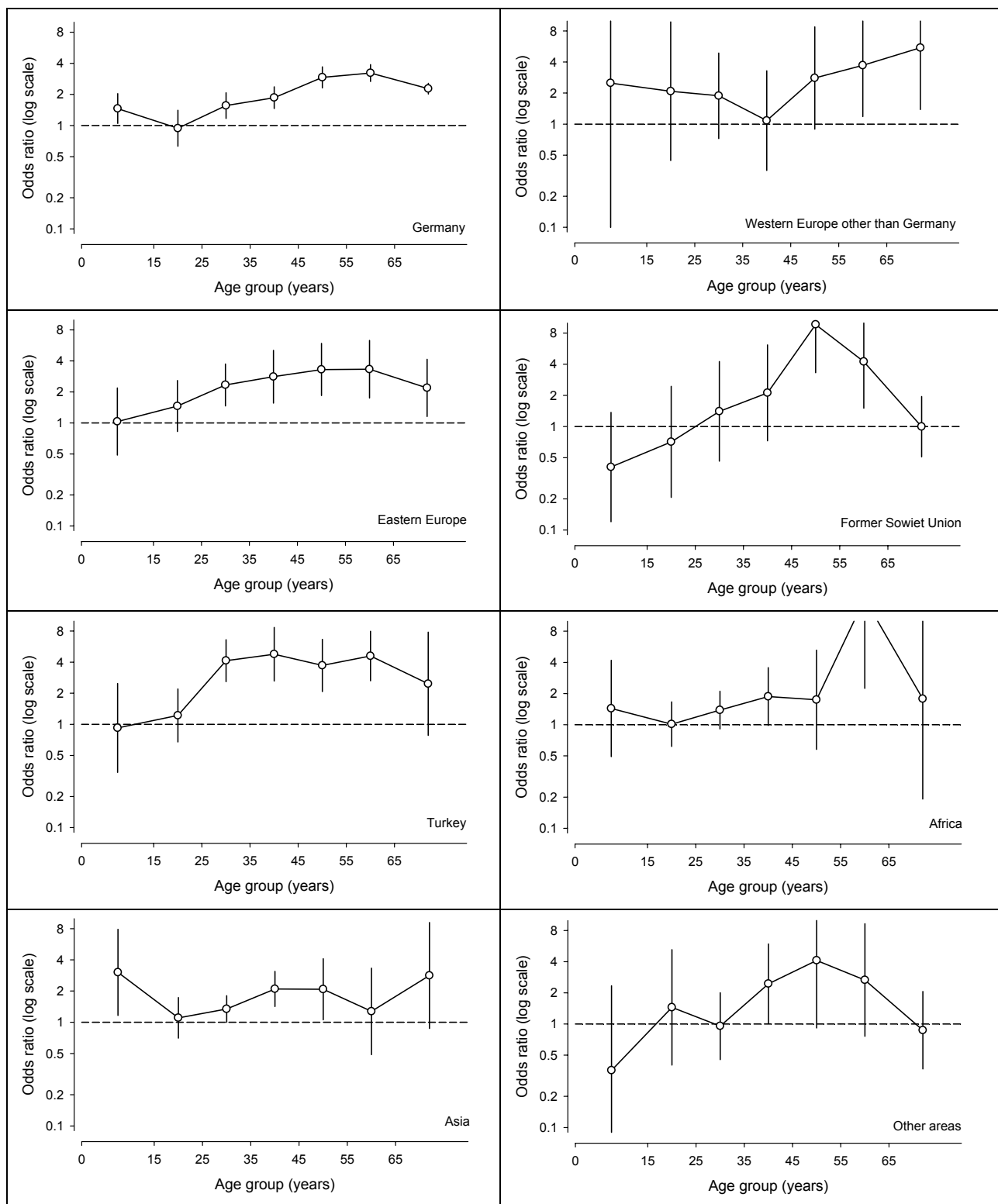


Figure 3.

