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Cohort Profile: Aussiedler Mortality (AMOR) – Cohort Study on Ethnic German Migrants from the Former Soviet Union

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Abstract

Purpose: The cohort represents the unique migrant group of ethnic Germans (resettlers) from the former Soviet Union who migrated to Germany mainly after 1989. Resettler are the second largest migrant group in Germany and their health status was largely unknown before this cohort was set up.

Participants: The retrospective cohort was set up in different federal states and consists of four subcohorts. In total, it includes 92,362 resettlers (men: 51.5%, women: 48.5%) who immigrated between 1990 and 2005. Mean age at immigration was 36.6 years (range 0-105 years).

Findings to date: Vital status and causes of death (ICD codes based on death certificates or record linkage) were collected as well as cancer incidence and incidence of AMI in two sub-cohorts. Currently, an observation period of 20 years (1990-2009) is covered. Overall mortality among resettlers was lower in comparison to the German population, especially for cardiovascular diseases. However, observed differences can neither be explained by the 'healthy migrant effect' nor by common behavioural risk factors and may be related to factors which have not yet been studied. Results on cancer incidence and mortality among resettlers confirm the very different risk profile with strongly elevated and reduced cancer-site specific risks. Analysis of to external causes of death such as suicide and drug abuse showed an elevated risk for male resettlers who migrated in teenage age and frequently changed residence within Germany.

Future plans: The existing cohort will be continued and prospective studies on resettlers are underway: One sub-cohort will be followed-up prospectively and two other large prospective cohort studies in Germany will be used for a detailed assessment of lifestyle, environmental and genetic/epigenetic factors on the mortality and morbidity pattern of resettlers.

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Article summary

Strengths and limitations of this study

- The retrospective cohort represents the unique migrant group of ethnic Germans (resettlers) from the former Soviet Union
- It includes 92,362 resettlers (men: 51.5%, women: 48.5%) who immigrated to Germany between 1990 and 2005
- sed ι. The register-based cohort covers an observation period of 20 years (1990-2009) and observed vital status and causes of death, as well as cancer incidence and incidence of AMI in

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Introduction

Studies on migrant populations contribute to knowledge on aetiology of diseases and reveal differences in the health status of migrants to the autochthonous population. The differences in the health status are often linked to different exposure profiles in migrants' respective country of origin, to the migration process itself, and to the integration process in the host country ¹⁻⁴. Furthermore, language barriers and cultural differences play an important role regarding health care utilization, which often differs among migrants compared to the host populations ⁵. Prominent examples of migrant cohorts are studies on Asian migrants in the U.S ⁶⁻⁸.

Migration is a worldwide phenomenon, driven by economic, social, and political reasons, along with enormous implications on individuals and societies. Although Germany has not typically been considered as a country of immigration, it has been welcoming migrants for decades. People with Turkish background and people with ethnic German background of Eastern European countries constitute by far the two largest migrant groups in Germany ⁹. Whereas Turkish migrants can partly be attributed to labour migration in the early 1960s, ethnic German migrants are a unique group of descendants of ethnic Germans. Since 1953, ethnic Germans and their families, including non-German spouses and their descendants, are allowed to move to Germany based on the Federal Expellee Law. These ethnic German migrants are legally called *Aussiedler* ("resettlers") or, since 1993, *Spätaussiedler* (literally "late resettlers"). To simplify matters, we will use the term "resettlers" for both groups. By law, upon arrival, resettlers are immediately granted the German citizenship with all rights and duties ¹⁰. In 2015, about 4% of the German population consisted of resettlers who had migrated themselves, coming from different Eastern European countries such as Romania, Poland and the Former Soviet Union (FSU) ¹⁰. Country-specific immigration patterns are closely linked to the political situation in the country of origin and displayed in figure 1.

→ Figure 1

Figure 1: Immigration of resettlers between 1950 and 2016 by country of origin ¹¹

Only few, however, moved before the breakdown of the Soviet Union and opening of the inner-German border in 1989, and most of them came from Poland. Since the fall of the Iron Curtain, resettlers' origin shifted almost exclusively to FSU countries. Originally, the ancestors of the FSU resettlers emigrated to the Russian empire in the 18th and 19th century, by invitation of the government. They were privileged compared to the Russian population, but at beginning of the 20th century they became victims of persecution and suffered increasing discrimination. Many ethnic Germans were deported to Kazakhstan and Siberia in 1941 when Nazi Germany launched the

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invasion of the Soviet Union and forced to work in agriculture. After the World War II their population recovered in the new settlement areas and many continued to preserve their distinct cultural identity. However, they were not allowed to return to their original places of residence ¹².

The AMOR cohort constitutes of resettlers from the FSU who immigrated since the collapse of the Soviet Union in 1990. Altogether, between 1990 and 2016 about 2.53 million resettlers, including spouses and descendants, immigrated to Germany, thereof 2.12 million resettlers from countries of the FSU ¹¹. As shown in figure 1, there was a large influx of resettlers between 1990 and 1994, which was more and more regulated in 1993 and 1996 by restricting the maximum number of immigrants accepted per year, and by a new legal requirement to prove German language skills already before departure, respectively ¹³ ¹⁴. Since 2005, the yearly number of arriving resettlers considerably decreased and remains low since. There are conflicting data on the total number of ethnic Germans living in the FSU before 1990. However, it is assumed that most of them have migrated to Germany which also explains the decrease in yearly numbers after 2005 ¹⁵. To avoid (self-) segregation, the German government assigned resettlers to a place of residence for at least two years based on a quasi-random procedure, considering population density and economic performance of the municipalities/counties ¹⁴.

\rightarrow Figure 2

Figure 2: Age-standardized all-cause mortality (European standard) of Russia, Kazakhstan and Germany since 1990¹⁶

Figure 2 displays age-standardized all-cause mortality rates of the FSU countries Russia and Kazakhstan and of Germany since 1990. Russia and Kazakhstan constitute the countries of origin of most of the resettlers from the FSU. Mortality in these countries was considerably higher compared to Germany. In Germany, mortality rates decreased steadily, but in Russia and Kazakhstan rates increased until 2003. In addition to higher all-cause mortality, differences in cardiovascular and external cause mortality were even more pronounced. There were also cancer-specific differences in incidence and mortality. For example, gastric cancer was and still is much more common in these Eastern European countries, whereas breast and prostate cancer incidence and mortality are lower than in Germany. Many of the differences can be explained by specific patterns of risk factors such as tobacco smoking and alcohol consumption, as well as poor diet and deteriorating public health care ¹⁷⁻¹⁹.

In 2004, the first cohort of resettlers from the FSU was set up in the federal state of North Rhine-Westphalia (NRW) to assess mortality patterns. Given the high mortality rates in FSU countries, the

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initial hypothesis was that resettlers import similar health profiles as observed in FSU countries, which would have demanded public health actions. Living conditions as well as lifestyle and behaviour among resettlers were assumed to be similar to those of the autochthonous populations in Russia and Kazakhstan. Further, resettlers were exposed to the same climatic conditions and had the same access to goods of daily life in the respective country. Based on that, the following hypotheses for a mortality comparison between resettlers and the German population were formulated:

- higher all-cause mortality among resettlers
- higher mortality due to cardiovascular diseases among resettlers
- cancer site-specific mortality differences between resettlers and the German population
- higher mortality due to external causes of death among resettlers.

In 2009 and 2014, the second and third cohort were initiated to specifically address cancer and cardiovascular diseases (CVD) incidence and mortality among resettlers. The second cohort was set up in the federal state of the Saarland and in close cooperation with the federal population-based cancer registry. The third cohort was based in the region of Augsburg in the federal state of Bavaria in cooperation with the local population-based myocardial infarction registry (MIR), which is part of the Cooperative Health Research in the Region of Augsburg (KORA) study platform. A fourth part of the cohort has recently been added in the administrative district of Münster, a part of NRW which also provides cancer incidence data since the early 1990s through a firstly local, and later federal, cancer registry. It is important to emphasise that the resettlers' German citizenship prevents their direct identification in German registry data such as civil registers or cause of death statistics. The setting-up of the first three parts of the AMOR cohort was funded by the German Research Foundation (DFG), the fourth cohort is funded by the German Cancer Aid.

Cohort description

All parts of the AMOR cohort consist of representative or full samples of resettlers from the FSU who immigrated after 1st January 1990 to the respective study areas. Characteristics of the cohorts are shown in table 1. Sex distribution, year of immigration and age at immigration pattern of the cohorts follow pattern seen in Germany-wide data on all immigrating FSU resettlers ^{20 21}.

Table 1: Characteristics of the AMOR cohorts including descriptive statistics

Inclusion criteria	NRW	Saarland	Augsburg	Münster	Total
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First residence	federal state	federal state	region of	Administrative	
(study area)	NRW	Saarland	Augsburg	district Münster	
((Bavaria)	(NRW)	
age at	>15 years	No restriction	No restriction	No restriction	
immigration	•	Notestriction	Notestriction	Norestriction	
immigration	1990-2001	1990-2005	1990-1999	1990-2001	1990-2005
period					
Main	Germany-wide	Germany-	Germany-wide	Münster-wide	
outcomes	cause-specific	wide cause-	cause-specific	cancer incidence	
	mortality	specific	mortality;		
		mortality;	Augsburg-wide		
		Saarland-wide	MI incidence		
		cancer			
		incidence			
Cooperating		Saarland	KORA study	NRW Cancer	
partners		Cancer	platform	Registry	
		Registry			
Participants	34,393	18,619	6,378	32,972	92,362
Men	16,734 (48.7%)	8,979 (48.2%)	3,031 (47.5%)	16,033 (48.6%)	44,777 (48.5%)
Women	17,659 (51.3%)	9,640 (51.8%)	3,347 (52.5%)	16,939 (51.4%)	47,585 (51.5%)
Year of					
immigration					
1990-1992	10,537 (30.6%)	5,168 (27.8%)	1,662 (26.1%)	9,363 (28.4%)	26,730 (28.9%)
1993-1995	11,211 (32.6%)	5,227 (28.1%)	2,199 (34.5%)	9,863 (29.9%)	28,500 (30.9%)
1996-1998	6,433 (18.7%)	3,930 (21.1%)	1,793 (28.1%)	8,344 (25.3%)	20,500 (22.2%)
1999+	6,212 (18.1%)	4,294 (23.1%)	724 (11.4%)	5,402 (16.4%)	16,632 (18.0%)
Age at					
immigration					
<18	2,151 (6.3%)	5,207 (28.0%)	2,178 (34.1%)	11,598 (35.2%)	21,134 (22.9%)
18-34	12,668 (36.8%)	5,325 (28.6%)	1,611 (25.3%)	9,217 (28.0%)	28,821 (31.2%)
35-64	15,820 (46.0%)	6,617 (35.5%)	2,118 (33.2%)	10,579 (32.1%)	35,134 (38.0%)
65+	3,754 (10.9%)	1,470 (7.9%)	471 (7.4%)	1,578 (4.8%)	7,273 (7.9%)

The NRW cohort is a sample of 34,393 individuals from all 281,356 resettlers who were assigned to the federal state of NRW between 1990 and 2001. They were at least 15 years of age at immigration and were and were full samples from municipalities/counties randomly selected from those which could access their population registries ²².

The Saarland cohort was established in cooperation with the Saarland cancer registry and aimed to incorporate FSU resettlers who immigrated between 1990 and 2005 and were assigned to the federal state of the Saarland ²³. It included all resettlers whose date of birth was available resulting in a sample of 18,619 individuals (64.2% of all resettlers). This cohort was focused on cancer incidence.

The cohort established in the region of Augsburg within the federal state of Bavaria consists of all FSU resettlers who have been allocated to local transition hostels in Augsburg between 1990 and 1999. This study was conducted in cooperation with the KORA study platform and the MIR of Augsburg ²⁴. Additional to capturing mortality data, the incidence of acute myocardial infarction

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(fatal and non-fatal cases) (AMI) was assessed for those living in the catchment area of the MIR. Further, in a subsample of resettlers a cross-sectional survey was performed, followed by a detailed physical and medical examination of their health status as well as their lifestyles.

The Münster cohort, which is currently under investigation, is a sample of 32,972 resettlers (53% of all resettlers) that could be identified in local registry offices who approved the identification procedure (50% of all local registries). The immigration period was between 1990 and 2001. In this study, cancer incidence data is collected in cooperation with the federal cancer registry of NRW.

Table 2 provides an overview of the descriptive follow-up results for each the retrospective, registerbased cohorts excluding the Münster cohort (follow-up ongoing). Vital status of the NRW cohort was already followed-up to three different time points, whereas the Saarland and the Augsburg cohort were followed-up once ²³⁻²⁷. Until today, all established cohorts cover an observation period for the mortality follow-up of 20 years. Cancer incidence of the Saarland cohort was followed-up twice and AMI incidence in the region of Augsburg once ²⁸⁻³⁰.

	NRW	Saarland	Augsburg
	(n=34,393)	(n=18,619)	(n=6,378)
Maximum observation period	1 Jan 1990 –	1 Jan 1990 –	1 Jan 1990 –
	31 Dec 2009	31 Dec 2009	31 May 2010
	Mortality follow	-up	
Completeness until Dec 2002	97.2%		
Alive	31,630 (92.0%)		
Deceased	1,805 (5.2%)		
Lost to follow-up	958 (2.8%)	2	
Person-years	251,377		
Completeness until Dec 2005	96.7%		
Alive	30,675 (89.2%)		
Deceased	2,580 (7.5%)		
Lost to follow-up	1,138 (3.3%)		
Person-years	344,486		
Completeness until Dec 2009	94.7%	95.1%	98.0%
Alive	28,790 (83.7%)	16,391 (88.0%)	5,781 (90.6%)
Deceased	3,789 (11.0%)	1,314 (7.1%)	469 (7.4%)
Lost to follow-up	1,814 (5.3%)	914 (4.9%)	128 (2.0%)
Person-years	465,396	243,369	90,095
Completeness of causes of	01.0%	91.6%	06.2%
death	91.9%	91.0%	96.2%
(C	ancer or AMI) Incidend	ce follow-up	
Until Dec 2005			
Incident cases		470 neoplasms ^a	
Person-years		176,588 ^b	
		1,0,000	

Table 2: Descriptive follow-up results of the AMOR cohorts (excluding Münster)

Until Dec 2009		
Incident cases	638 neoplasms ^a	86 AMI
Person-years	204,366	51,077

^a all malignant neoplasms except non-melanoma skin cancer (ICD-10: C44) ^b estimated based on ³¹

The three AMOR cohorts NRW, Saarland, and Augsburg used the same register-based procedure to assess the vital status of the cohort members as well as the cause of death of all deceased members. Vital status was ascertained Germany-wide through local population registries by record linkage or manually. Individuals who changed residence were followed up subsequently through local population registries and censored when moving out of Germany or at their last known date of moving, deceased participants at the date of death. For deceased cohort members, date and place of death was collected, and after deleting individuals' identifying information the cause of death was provided by local health authorities in an anonymized death certificate or electronically by using record linkage. All causes of death were coded according to the International Classification of Diseases (ICD) edition 9 (until 1997) or edition 10 (since 1998).

Cancer incidence data of the Saarland cohort was provided by the Saarland Cancer Registry through record linkage using phonetic code of first and last name, sex, date of birth and city of residence. In the Münster cohort a different record linkage procedure was applied. In addition to the standard record linkage system using a stochastic method, a thesaurus of common changes of the first and last name when transcribing them from Kyrillic to German alphabet was used to identify all incident cancer cases among cohort members. Thereby, probability-based weights were assigned to pairs of records ³². The thesaurus was built on the information collected from the other three cohorts and was intended to increase the success rate of the record linkage.

The MIR provides data on incidence of AMIs for individuals in the region of Augsburg between age 25 and 74 from with an estimated 95% completeness of case finding ³³. Cohort members affected by AMIs were identified by record linkage based on sex, initials of the names and date of birth. For the incidence follow-up cohort members were censored when they moved out of the MIR catchment area.

In addition to the above described record linkages to routine data sources for morbidity and mortality, further studies have been nested into the AMOR cohorts. A list of these studies, also containing the phase when the respective study was nested, is provided in table 3. A nested case-control study was performed within the NRW cohort after the follow-up until 2005 ³⁴. Relatives of cohort members who died from CVD and controls themselves were interviewed by telephone using a standardized questionnaire. The aim was to identify and to quantify CVD risk factors. A nested cross-

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sectional study was conducted within a random sample of the Saarland cohort after the incidence follow-up of 2005 and during the mortality follow-up. The aim was to assess drug consumption, handling and administering drugs in the light of reported health status and sociodemographic characteristics ³⁵. Another nested cross-sectional study was conducted within the Augsburg cohort in 2012. First, a questionnaire-based survey was applied to all resettlers alive in 2010 and still living in Augsburg region (N=3,742, 16% response). Second, the respondents of the questionnaire were invited to a detailed physical and medical examination and to provide a blood sample (N=189, 32% response).

Table 3: List of studies nested into the different AMOR cohorts

	NRW	Saarland	Augsburg
After the follow-	nested case-control	nested cross-sectional	
up until 2005	study (n=348): CVD	study (n=114): drug	
	risk factors	utilization	
	(interviews)	(questionnaires)	
After the follow-	N.		cross-sectional survey (n=595):
up until 2009			lifestyle, immigration
(Augsburg until			background, morbidity, mental
May 2010)			health, health care
			(questionnaires);
			cross-sectional study (n=189):
			detailed lifestyle, detailed
			immigration background,
			detailed medical examination,
			interviews, blood sample

Patient and Public Involvement

Since information on cause of death as well as incidence of cancer and of AMI was retrieved anonymously by registry data, patients were not involved. For the collection on CVD risk factors, on drug utilization and for the cross-sectional survey, individuals of the respective samples were first contacted by mail with information on the aims of the study. Later individuals who agreed to participate were either contacted by phone (NRW) or again by mail (Saarland) or involved to the study centre (Augsburg). The public was not involved in the study.

Findings to date

Results of the AMOR cohorts show that the overall mortality among resettlers from the FSU was not only lower than in the countries of the FSU, but also lower in comparison to the German population. This was especially pronounced in CVD mortality. However, it has been shown that relevant CVD risk factors such as hyperlipidaemia, obesity, tobacco smoking (among men), low physical activity and

non-participation in screening programs are more prevalent among resettlers ³⁴⁻³⁶. So far, observed differences cannot be explained and may be related to factors which have not yet been studied.

It is important to highlight that resettlers are a unique group of migrants and a 'healthy migrant effect', which is observed in many migrant studies, is rather unlikely. Resettlers were hardly selected, in fact they are invited to Germany and receive German citizenship upon arrival. They immediately have full access to the German health care system, which might also have been a motivation for sick family members to migrate. This assumption is supported by deaths observed shortly after immigration. Furthermore, resettlers mostly immigrated with their complete family.

Results on cancer incidence and mortality among resettlers confirm a very different risk profile in comparison to the German population. For example, gastric cancer is strongly elevated among resettlers and within the observation time hardly attenuates to German rates ^{23 26}. Furthermore, it was shown that the high incidence among resettlers cannot be explained by the assumed higher prevalence of Helicobacter pylori, but is strongly associated with lifestyle and dietary factors ³⁷.

Since the allocation of the resettlers was done quasi-randomly within Germany, the cohort allowed to investigate the effect of regional deprivation on individual mortality by making use of a natural experiment. The NRW sub-cohort was used to assign each individual into one of six geographical deprivation clusters and found SMR highest in the cluster "poverty poles" ³⁸.

Analysis within the cohorts of the AMOR studies were also done with respect to external causes of death such as suicide and drug abuse. Here, an elevated risk was found especially for male resettlers who migrated in teenage age and frequently changed residence within Germany ³⁹.

Table 4 presents a comparison of cause-specific mortality among resettlers and the German population for the whole observation period between 1990 and 2009 for all cohorts combined as standardized mortality ratios (SMR).

Cause of death	W	omen	Men	
(ICD-10 code)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes	2,674	0.87 (0.84-0.91)	2,898	0.96 (0.92-0.99)
All CVD (100-199)	1,184	0.84 (0.79-0.89)	934	0.80 (0.75-0.86)
Ischaemic heart diseases (120-125)	418	0.80 (0.72-0.88)	451	0.79 (0.72-0.87)
Cerebrovascular diseases (160-169)	258	0.84 (0.74-0.95)	178	0.89 (0.77-1.03)
All cancer*	669	0.84 (0.78-0.91)	864	1.00 (0.94-1.07)

Table 4: Cause-specific standardized mortality ratios (SMR) with 95% confidence limits (95% CI) of resettlers in comparison to the general German population

(C00-C97)				
Stomach (C16)	66	1.52 (1.19-1.93)	84	1.62 (1.31-2.01)
Colorectal (C18-C21)	92	0.86 (0.70-1.05)	77	0.74 (0.59-0.93)
Lung (C33-C34)	62	0.69 (0.54-0.88)	307	1.34 (1.20-1.50)
Female breast (C50)	82	0.55 (0.44-0.68)		
Prostate (C61)			46	0.58 (0.43-0.77)
All external causes (V01-Y84)	59	0.57 (0.44-0.73)	219	1.03 (0.90-1.18)
Accident (V01-X59)	31	0.48 (0.34-0.68)	73	0.65 (0.52-0.82)
Suicide (X60-X84)	13	0.44 (0.26-0.77)	82	1.00 (0.80-1.24)
Events of undetermined intent (Y10-Y34)	8	1.10 (0.47-2.16)	35	2.45 (1.71-3.40)
All unknown/ill- defined (R00-R99)	109	1.44 (1.19-1.74)	160	1.80 (1.54-2.10)

* except non-melanoma skin cancer (ICD-10: C44)

Strengths and limitations

The main strengths of the AMOR studies are the large representative samples of this unique group of migrants which is hard to identify in register-based data, and the high completeness of follow-up for an observation period of 20 years. All resettlers are registered within the high-quality registration system of German, which reduces the likelihood of out-migration bias. Main outcomes are based on information from health authorities and high-quality registries.

Main weaknesses arise from the fact that all cohorts are based on secondary data only. There is no individual information on risk factors or sociodemographic information other than what is available from the registries. The nested case-control and cross-sectional studies are all limited by the relatively low response of this migrant group.

Further prospective studies on resettlers are underway. (i) A sample of the Augsburg cohort will be followed-up prospectively and use the cross-sectional study as its baseline. (ii) There are currently two large prospective cohort studies in Germany in the recruitment phase, the National Cohort ⁴⁰ and the Hamburg City Health study. These studies plan to recruit 200,000 and 45,000 individuals, respectively. Since the response has been found to be similar in resettlers and autochthone Germans, we expect approximately 2% of the study populations to be resettlers, i.e. approximately 5,000 individuals ⁴¹. This sample will allow a detailed assessment of lifestyle, environmental and genetic/epigenetic factors on their mortality and morbidity pattern.

Collaboration

Data of the AMOR studies are not open access, but we encourage other researchers to contact us and apply for data access based on collaborating projects. Please, contact Prof. Dr. Heiko Becher (h.becher@uke.de) or PD Dr. Volker Winkler (v.winkler@uni-heidelberg.de) to apply for possible collaborations.

Further details

Funding declaration

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Competing interests

The authors state no competing interests.

Data sharing statement

We welcome collaboration and the data will be shared with investigators. External researchers can get access to the AMOR data through collaborating projects. Please contact Prof. Dr. Heiko Becher (h.becher@uke.de) or PD Dr. Volker Winkler (v.winkler@uni-heidelberg.de)

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Contributorship statement

VW wrote the manuscript, collected part of the data and is co-PI of the study. SK, AD and VL collected parts of the data and contributed to writing of the manuscript. BH and CM enabled part of the record linkage procedures, helped with data collection and gave critical feedback to manuscript. OR and HB initiated the study and significantly contributed to writing. HB is the PI of the study.

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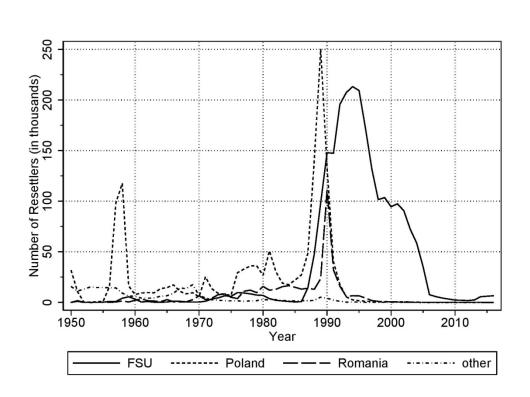
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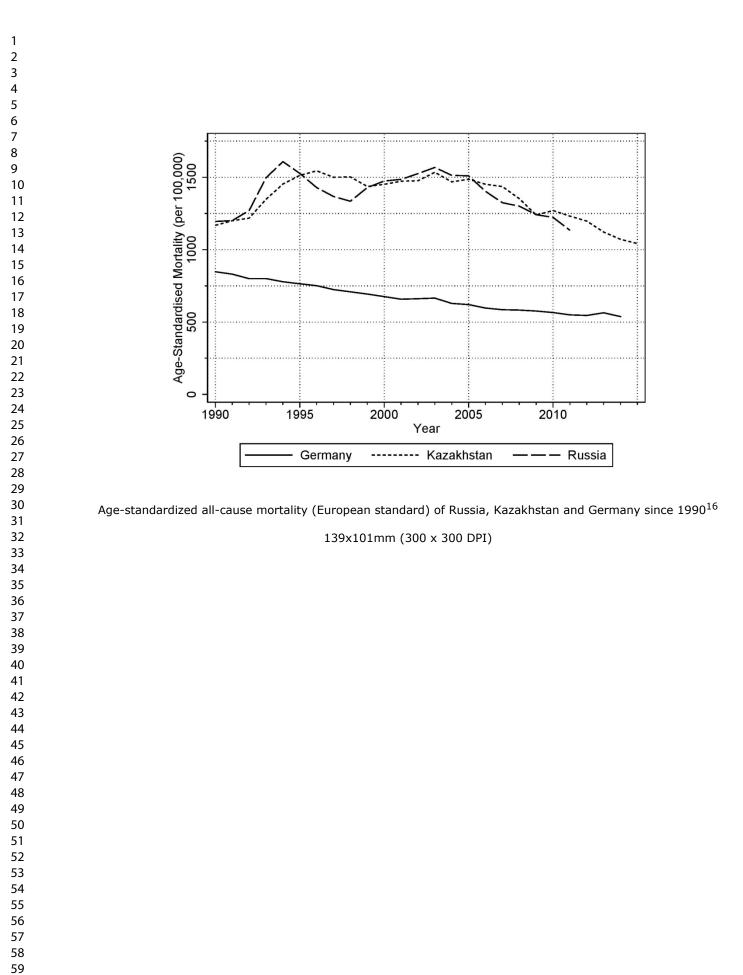
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Immigration of resettlers between 1950 and 2016 by country of origin¹¹

139x101mm (300 x 300 DPI)



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Cohort Profile: Aussiedler Mortality (AMOR) – Cohort Studies on Ethnic German Migrants from the Former Soviet Union

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Abstract

Purpose: The AMOR cohorts represent the unique migrant group of ethnic Germans (resettlers) from the former Soviet Union who migrated to Germany mainly after the fall of the iron curtain in 1989. Resettlers are the second largest migrant group in Germany and their health status was largely unknown before the cohorts were set up.

Participants: Four retrospective register-based cohorts were set up in different federal statesof Germany each focussing on different health aspects. In total, the cohorts include 92,362 resettlers (men: 51.5%, women: 48.5%) who immigrated between 1990 and 2005 with a mean age at immigration of 36.6 years (range 0-105 years). Resettlers are of German ancestry and they are immediately granted the German citizenship with all rights and duties.

Findings to date: Vital status and causes of death (ICD codes based on death certificates or record linkage) were collected for thee cohorts as well as cancer incidence and incidence of Acute myocardial infarction in three of the cohorts. Currently, an observation period of 20 years (1990-2009) is covered. Overall mortality among resettlers was surprisingly lower in comparison to the German population with standardized mortality ratios of 0.87 (95% confidence limits: 0.84-0.91) for females and 0.96 (0.92-0.99) for males, and even stronger for cardiovascular diseases (females: 0.84 (079-0.89); males: 0.80 (0.75-0.86). However, observed differences can neither be explained by the 'healthy migrant effect' nor by common behavioural risk factors and may be related to factors which have not yet been studied.

Future plans: The existing cohorts will be continued and prospective studies on resettlers are underway: One cohort will be followed-up prospectively and two other large prospective cohort studies in Germany will be used for a detailed assessment of lifestyle, environmental and genetic/epigenetic factors on the mortality and morbidity pattern of resettlers.



Article summary

Strengths and limitations of this study

- The four retrospective cohorts represent the unique migrant group of ethnic Germans (resettlers) from the former Soviet Union
- They include 92,362 resettlers (men: 51.5%, women: 48.5%) who immigrated to Germany between 1990 and 2005
- The register-based cohorts cover an observation period of 20 years (1990-2009) and observed vital status and causes of death, as well as cancer incidence and incidence of AMI
- Since the cohorts are utilizing secondary data, there is no individual information on risk factors or sociodemographic information.
- The nested case-control and cross-sectional studies are limited due to relatively low response

Introduction

Studies on migrant populations contribute to knowledge on aetiology of diseases and reveal differences in the health status of migrants compared with the autochthonous population. The differences in the health status are often linked to different exposure profiles in migrants' respective country of origin, to the migration process itself, and to the integration process in the host country.¹⁻⁴ Furthermore, language barriers and cultural differences play an important role regarding health care utilization, which often differs among migrants compared to the host populations.⁵ Prominent examples of migrant cohorts are studies on Asian migrants in the U.S.⁶⁻⁸

Migration is a worldwide phenomenon, driven by economic, social, and political reasons, along with enormous implications on individuals and societies. Although Germany has not typically been considered as a country of immigration, it has been welcoming migrants for decades. People with Turkish background and people with ethnic German background of Eastern European countries constitute by far the two largest migrant groups in Germany.⁹ Whereas Turkish migrants can partly be attributed to labour migration in the early 1960s, ethnic German migrants are a unique group of descendants of ethnic Germans. Since 1953, ethnic Germans and their families, including non-German spouses and their descendants, are allowed to move to Germany based on the Federal Expellee Law. These ethnic German migrants are legally called *Aussiedler* ("resettlers") or, since 1993, *Spätaussiedler* (literally "late resettlers"). To simplify matters, we will use the term "resettlers" for both groups. By law, upon arrival, resettlers are immediately granted the German citizenship with all rights and duties.¹⁰ In 2015, about 4% of the German population consisted of resettlers who had migrated themselves, coming from different Eastern European countries such as Romania, Poland and the Former Soviet Union (FSU).¹⁰ Country-specific immigration patterns are closely linked to the political situation in the country of origin and displayed in figure 1.

\rightarrow Figure 1

Figure 1: Immigration of resettlers between 1950 and 2016 by country of origin¹¹

Only few, however, moved before the breakdown of the Soviet Union and opening of the inner-German border in 1989, and most of them came from Poland. Since the fall of the Iron Curtain, resettlers' origin shifted almost exclusively to FSU countries. Originally, the ancestors of the FSU resettlers emigrated to the Russian empire in the 18th and 19th century, by invitation of the government. They were privileged compared to the Russian population, but at beginning of the 20th century they became victims of persecution and suffered increasing discrimination. Many ethnic Germans were deported to Kazakhstan and Siberia in 1941 when Nazi Germany launched the invasion

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of the Soviet Union and forced to work in agriculture. After the World War II their population recovered in the new settlement areas and many continued to preserve their distinct cultural identity. However, they were not allowed to return to their original places of residence.¹²

The AMOR cohorts constitute of resettlers from the FSU who immigrated since the collapse of the Soviet Union in 1990. Altogether, between 1990 and 2016 about 2.53 million resettlers, including spouses and descendants, immigrated to Germany, thereof 2.12 million resettlers from countries of the FSU.¹¹ As shown in figure 1, there was a large influx of resettlers between 1990 and 1994, which was more and more regulated in 1993 and 1996 by restricting the maximum number of immigrants accepted per year, and by a new legal requirement to prove German language skills already before departure, respectively.¹³ ¹⁴ Since 2005, the yearly number of arriving resettlers considerably decreased and remains low since. There are conflicting data on the total number of ethnic Germans living in the FSU before 1990. However, it is assumed that most of them have migrated to Germany which also explains the decrease in yearly numbers after 2005.¹⁵ To avoid (self-) segregation, the German government assigned resettlers to a place of residence for at least two years based on a quasirandom procedure, considering population density and economic performance of the municipalities/counties.¹⁴

\rightarrow Figure 2

Figure 2: Age-standardized all-cause mortality (European standard) of Russia, Kazakhstan and Germany since 1990¹⁶

Figure 2 displays age-standardized all-cause mortality rates of the FSU countries Russia and Kazakhstan and of Germany since 1990. Russia and Kazakhstan constitute the countries of origin of most of the resettlers from the FSU. Mortality in these countries was considerably higher compared to Germany. In Germany, mortality rates decreased steadily, but in Russia and Kazakhstan rates increased until 2003. In addition to higher all-cause mortality, differences in cardiovascular and external cause mortality were even more pronounced. There were also cancer-specific differences in incidence and mortality. For example, gastric cancer was and still is much more common in these Eastern European countries, whereas breast and prostate cancer incidence and mortality are lower than in Germany. Many of the differences can be explained by specific patterns of risk factors such as tobacco smoking and alcohol consumption, as well as poor diet and deteriorating public health care.¹⁷⁻¹⁹

In 2004, the first cohort of resettlers from the FSU was set up in the federal state of North Rhine-Westphalia (NRW) to assess mortality patterns. Given the high mortality rates in FSU countries, the initial hypothesis was that resettlers import similar health profiles as observed in FSU countries, which would have demanded public health actions. Living conditions as well as lifestyle and behaviour among resettlers were assumed to be similar to those of the autochthonous populations in Russia and Kazakhstan. Further, resettlers were exposed to the same climatic conditions and had the same access to goods of daily life in the respective country. Based on that, the following hypotheses for a mortality comparison between resettlers and the German population were formulated:

- higher all-cause mortality among resettlers
- higher mortality due to cardiovascular diseases among resettlers
- cancer site-specific mortality differences between resettlers and the German population
- higher mortality due to external causes of death among resettlers.

In 2009 and 2014, the second and third cohort were initiated to specifically address cancer and cardiovascular diseases (CVD) incidence and mortality among resettlers. The second cohort was set up in the federal state of the Saarland and in close cooperation with the federal population-based cancer registry. The third cohort was based in the region of Augsburg in the federal state of Bavaria in cooperation with the local population-based myocardial infarction registry (MIR), which is part of the Cooperative Health Research in the Region of Augsburg (KORA) study platform. A fourth cohort has recently been added in the administrative district of Münster, a part of NRW which also provides cancer incidence data since the early 1990s through a firstly local, and later federal, cancer registry. It is important to emphasise that the resettlers' German citizenship prevents their direct identification in German registry data such as civil registers or cause of death statistics. The setting-up of the first three AMOR cohorts were funded by the German Research Foundation (DFG), the fourth cohort is funded by the German Cancer Aid.

Cohort description

All AMOR cohorts consist of representative or full samples of resettlers from the FSU who immigrated after 1st January 1990 to the respective study areas. Characteristics of the cohorts are shown in table 1. Sex distribution, year of immigration and age at immigration pattern of the cohorts follow pattern seen in Germany-wide data on all immigrating FSU resettlers.^{20 21}

Inclusion criteria	NRW	Saarland	Augsburg	Münster	Total
First residence (study area)	federal state NRW	federal state Saarland	region of Augsburg	Administrative district Münster	
			(Bavaria)	(NRW)	

Table 1: Characteristics of the AMOR cohorts including descriptive statistics

age at immigration	>15 years	No restriction	No restriction	No restriction	
immigration period	1990-2001	1990-2005	1990-1999	1990-2001	1990-2005
Main	Germany-wide	Germany-	Germany-wide	Münster-wide	
outcomes	cause-specific	wide cause-	cause-specific	cancer incidence	
	mortality	specific	mortality;		
		mortality;	Augsburg-wide		
		Saarland-wide	MI incidence		
		cancer			
		incidence			
Cooperating	-	Saarland	KORA study	NRW Cancer	
partners		Cancer	platform	Registry	
		Registry			
Participants	34,393	18,619	6,378	32,972	92,362
Men	16,734 (4 <mark>8</mark> .7%)	8,979 (48.2%)	3,031 (47.5%)	16,033 (48.6%)	44,777 (48.5%)
Women	17,659 (51.3%)	9,640 (51.8%)	3,347 (52.5%)	16,939 (51.4%)	47,585 (51.5%)
Year of					
immigration					
1990-1992	10,537 (30.6%)	5,168 (27.8%)	1,662 (26.1%)	9,363 (28.4%)	26,730 (28.9%)
1993-1995	11,211 (32.6%)	5,227 (28.1%)	2,199 (34.5%)	9,863 (29.9%)	28,500 (30.9%)
1996-1998	6,433 (18.7%)	3,930 (21.1%)	1,793 (28.1%)	8,344 (25.3%)	20,500 (22.2%)
1999+	6,212 (18.1%)	4,294 (23.1%)	724 (11.4%)	5,402 (16.4%)	16,632 (18.0%)
Age at immigration					
<18	2,151 (6.3%)	5,207 (28.0%)	2,178 (34.1%)	11,598 (35.2%)	21,134 (22.9%)
18-34	12,668 (36.8%)	5,325 (28.6%)	1,611 (25.3%)	9,217 (28.0%)	28,821 (31.2%)
35-64	15,820 (46.0%)	6,617 (35.5%)	2,118 (33.2%)	10,579 (32.1%)	35,134 (38.0%)
65+	3,754 (10.9%)	1,470 (7.9%)	471 (7.4%)	1,578 (4.8%)	7,273 (7.9%)

The NRW cohort is a sample of 34,393 individuals from all 281,356 resettlers who were assigned to the federal state of NRW between 1990 and 2001. Information on all resettlers were available from the central reception centre of NRW. Sampled resettlers were at least 15 years of age at immigration and their first residence had been assigned to municipalities/counties with electronic population registries. The 34,393 resettlers represent 91% of all resettlers of the respective municipalities/counties. Since assignment to the different municipalities within a state was done on a random basis, the selected cohort constitutes a random sample of all resettlers.²²

The Saarland cohort was established in cooperation with the Saarland cancer registry and aimed to incorporate FSU resettlers who immigrated between 1990 and 2005 and were assigned to the federal state of the Saarland.²³Resettlers were identified by collecting application forms on obtaining German passports in all local refugee offices of the Saarland. The cohort included all resettlers whose date of birth was available resulting in a sample of 18,619 individuals (64.2% of all resettlers). This cohort was focused on cancer incidence.

The cohort established in the region of Augsburg within the federal state of Bavaria consists of all FSU resettlers who have been allocated to local transition hostels in Augsburg between 1990 and 1999 where all resettlers have first assigned to. This study was conducted in cooperation with the KORA study platform and the MIR of Augsburg.²⁴ Additional to capturing mortality data, the incidence of acute myocardial infarction (fatal and non-fatal cases) (AMI) was assessed for those living in the catchment area of the MIR. Further, in a subsample of resettlers a cross-sectional survey was performed, followed by a detailed physical and medical examination of their health status as well as their lifestyles.

The Münster cohort, where the follow-up is still ongoing, is a sample of 32,972 resettlers (53% of all resettlers) that could be identified in local registry offices who approved the identification procedure (50% of all local registries). The immigration period was between 1990 and 2001. In this study, cancer incidence data is collected in cooperation with the federal cancer registry of NRW.

All cohorts reflect expected distributions of sex, year and age of immigration when compared to national statistics of immigrated resettlers which indicates that the cohorts are representative for this migrant group.

Table 2 provides an overview of the descriptive follow-up results for each the retrospective, registerbased cohorts excluding the Münster cohort (follow-up ongoing). Vital status of the NRW cohort was already followed-up to three different time points, whereas the Saarland and the Augsburg cohort were followed-up once.²³⁻²⁷ Until today, all established cohorts cover an observation period for the mortality follow-up of 20 years. Cancer incidence of the Saarland cohort was followed-up twice and AMI incidence in the region of Augsburg once.²⁸⁻³⁰

	NRW	Saarland	Augsburg
	(n=34,393)	(n=18,619)	(n=6,378)
Maximum observation period	1 Jan 1990 –	1 Jan 1990 –	1 Jan 1990 –
	31 Dec 2009	31 Dec 2009	31 May 2010
	Mortality follow	r-up	
Completeness until Dec 2002	97.2%		
Alive	31,630 (92.0%)		
Deceased	1,805 (5.2%)		
Lost to follow-up	958 (2.8%)		
Person-years	251,377		
Completeness until Dec 2005	96.7%		
Alive	30,675 (89.2%)		
Deceased	2,580 (7.5%)		
Lost to follow-up	1,138 (3.3%)		

Table 2: Descriptive follow-up results of the AMOR cohorts (excluding Münster)

Person-years	344,486		
Completeness until Dec 2009	94.7%	95.1%	98.0%
Alive	28,790 (83.7%)	16,391 (88.0%)	5,781 (90.6%)
Deceased	3,789 (11.0%)	1,314 (7.1%)	469 (7.4%)
Lost to follow-up	1,814 (5.3%)	914 (4.9%)	128 (2.0%)
Person-years	465,396	243,369	90,095
Completeness of causes of death	91.9%	91.6%	96.2%
(Ca	ancer or AMI) Incidend	ce follow-up	
Until Dec 2005			
Incident cases		470 neoplasms ^a	
Person-years		176,588 ^b	
Until Dec 2009			
Incident cases		638 neoplasms ^a	86 AMI
Person-years		204,366	51,077

^a all malignant neoplasms except non-melanoma skin cancer (ICD-10: C44)

^b estimated based on³¹

The three AMOR cohorts NRW, Saarland, and Augsburg used the same register-based procedure to assess the vital status of the cohort members as well as the cause of death of all deceased members. Vital status was ascertained Germany-wide through local population registries by record linkage or manually. Individuals who changed residence were followed up subsequently through local population registries and censored when moving out of Germany or at their last known date of moving, deceased participants at the date of death. For deceased cohort members, date and place of death was collected, and after deleting individuals' identifying information the cause of death was provided by local health authorities in an anonymized death certificate or electronically by using record linkage. All causes of death were coded according to the International Classification of Diseases (ICD) edition 9 (until 1997) or edition 10 (since 1998).

Cancer incidence data of the Saarland cohort was provided by the Saarland Cancer Registry through record linkage using phonetic code of first and last name, sex, date of birth and city of residence. In the Münster cohort a different record linkage procedure was applied. In addition to the standard record linkage system using a stochastic method, a thesaurus of common changes of the first and last name when transcribing them from Kyrillic to German alphabet was used to identify all incident cancer cases among cohort members. Thereby, probability-based weights were assigned to pairs of records.³² The thesaurus was built on the information collected from the other three cohorts and was intended to increase the success rate of the record linkage.

The MIR provides data on incidence of AMIs for individuals in the region of Augsburg between age 25 and 74.³³ Cohort members affected by AMIs were identified by record linkage based on sex, initials of

the names and date of birth. For the incidence follow-up cohort members were censored when they moved out of the MIR catchment area and at age 75.

In addition to the above described record linkages to routine data sources for morbidity and mortality, further studies have been nested into the AMOR cohorts. A list of these studies, also containing the phase when the respective study was nested, is provided in table 3. A nested case-control study (N=348, 38% response) was performed within the NRW cohort after the follow-up until 2005.³⁴ Relatives of cohort members who died from CVD and controls themselves were interviewed by telephone using a standardized questionnaire. The aim was to identify and to quantify CVD risk factors. A nested cross-sectional study (N=114, 16% response) was conducted within a random sample of the Saarland cohort after the incidence follow-up of 2005 and during the mortality follow-up. The aim was to assess drug consumption, handling and administering drugs in the light of reported health status and sociodemographic characteristics.³⁵ Another nested cross-sectional study was conducted within the Augsburg cohort in 2012. First, a questionnaire-based survey was applied to all resettlers alive in 2010 and still living in Augsburg region (N=3,742, 16% response). Second, the respondents of the questionnaire were invited to a detailed physical and medical examination and to provide a blood sample (N=189, 32% response).

	NRW	Saarland	Augsburg
After the follow-	nested case-control	nested cross-sectional	
up until 2005	study (n=348): CVD	study (n=114): drug	
	risk factors	utilization	
	(interviews)	(questionnaires)	
After the follow-			cross-sectional survey (n=595):
up until 2009			🔰 🚽 lifestyle, immigration
(Augsburg until			background, morbidity, mental
May 2010)			health, health care
			(questionnaires);
			cross-sectional study (n=189):
			detailed lifestyle, detailed
			immigration background,
			detailed medical examination,
			interviews, blood sample

Table 3: List of studies nested into the different AMOR cohorts

Patient and Public Involvement

Since information on cause of death as well as incidence of cancer and of AMI was retrieved anonymously by registry data, patients were not involved. For the collection on CVD risk factors, on drug utilization and for the cross-sectional survey, individuals of the respective samples were first contacted by mail with information on the aims of the study. Later individuals who agreed to

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participate were either contacted by phone (NRW) or again by mail (Saarland) or involved to the study centre (Augsburg). By signing a consent form or by a telephone call, the participants declared willingness to participate in the nested studies presented in table 3 and assured that they were informed sufficiently on the study and the further use of the data collected. Participation could be withdrawn at any time. The public was not involved in the study.

Findings to date

Results of the AMOR cohorts show that the overall mortality among resettlers from the FSU was not only lower than in the countries of the FSU, but also lower in comparison to the German population. This was especially pronounced in CVD mortality. However, it has been shown that relevant CVD risk factors such as hyperlipidaemia, obesity, tobacco smoking (among men), low physical activity and nonparticipation in screening programs are more prevalent among resettlers.³⁴⁻³⁶ Given the limited knowledge which also arises from the generally low response of this group to actively take part in studies, the observed differences cannot be explained and may even be related to factors which have not yet been studied.

It is important to highlight that resettlers are a unique group of migrants and a 'healthy migrant effect', which is observed in many migrant studies, is rather unlikely. Resettlers were hardly selected, in fact they are invited to Germany and receive German citizenship upon arrival. They immediately have full access to the German health care system, which might also have been a motivation for sick family members to migrate. This assumption is supported by deaths observed shortly after immigration. Furthermore, resettlers mostly immigrated with their complete family.

Results on cancer incidence and mortality among resettlers confirm a very different risk profile in comparison to the German population. For example, gastric cancer is strongly elevated among resettlers and within the observation time hardly attenuates to German rates.^{23 26} Furthermore, it was shown that the high incidence among resettlers cannot be explained by the assumed higher prevalence of Helicobacter pylori, but is strongly associated with lifestyle and dietary factors.³⁷

Since the allocation of the resettlers was done quasi-randomly within Germany, the cohort allowed to investigate the effect of regional deprivation on individual mortality by making use of this natural experiment. The NRW cohort was used to assess the effect of regional deprivation on individual mortality by aggregating the 54 counties of NRW in six deprivation clusters. Standardized mortality ratios (SMRs) comparing resettler mortality with to the mortality of the autochthonous population resulted in highest SMRs for regions with the highest level of regional deprivation.³⁸

Analysis within the cohorts of the AMOR studies were also done with respect to external causes of death such as suicide and drug abuse. Here, an elevated risk was found especially for male resettlers who migrated in teenage age and frequently changed residence within Germany.³⁹

Table 4 presents a comparison of cause-specific mortality among resettlers and the German population for the whole observation period between 1990 and 2009 for all cohorts combined (excluding the Münster cohort) as SMRs.

Table 4: Cause-specific standardized mortality ratios (SMR) with 95% confidence limits (95% CI) of resettlers in comparison to the general German population

Cause of death	Wo	men	M	en
(ICD-10 code)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes	2,674	0.87 (0.84-0.91)	2,898	0.96 (0.92-0.99)
All CVD (100-199)	1,184	0.84 (0.79-0.89)	934	0.80 (0.75-0.86)
Ischaemic heart diseases (120-125)	418	0.80 (0.72-0.88)	451	0.79 (0.72-0.87)
Cerebrovascular diseases (160-169)	258	0.84 (0.74-0.95)	178	0.89 (0.77-1.03)
All cancer* (C00-C97)	669	0.84 (0.78-0.91)	864	1.00 (0.94-1.07)
Stomach (C16)	66	1.52 (1.19-1.93)	84	1.62 (1.31-2.01)
Colorectal (C18-C21)	92	0.86 (0.70-1.05)	77	0.74 (0.59-0.93)
Lung (C33-C34)	62	0.69 (0.54-0.88)	307	1.34 (1.20-1.50)
Female breast (C50)	82	0.55 (0.44-0.68)	0	
Prostate (C61)			46	0.58 (0.43-0.77)
All external causes (V01-Y84)	59	0.57 (0.44-0.73)	219	1.03 (0.90-1.18)
Accident (V01-X59)	31	0.48 (0.34-0.68)	73	0.65 (0.52-0.82)
Suicide (X60-X84)	13	0.44 (0.26-0.77)	82	1.00 (0.80-1.24)
Events of undetermined intent (Y10-Y34)	8	1.10 (0.47-2.16)	35	2.45 (1.71-3.40)
All unknown/ill- defined (R00-R99)	109	1.44 (1.19-1.74)	160	1.80 (1.54-2.10)

* except non-melanoma skin cancer (ICD-10: C44)

Strengths and limitations

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 The main strengths of the AMOR studies are the large representative samples of this unique group of migrants which is hard to identify in register-based data, and the high completeness of follow-up for an observation period of 20 years. All resettlers are registered within the high-quality registration system of German, which reduces the likelihood of out-migration bias. Main outcomes are based on information from health authorities and high-quality registries.

Main weaknesses arise from the fact that all cohorts are based on secondary data only. There is no individual information on risk factors or sociodemographic information other than what is available from the registries. The nested case-control and cross-sectional studies are all limited by the relatively low response of this migrant group.

Further prospective studies on resettlers are underway. (i) A sample of the Augsburg cohort will be followed-up prospectively and use the cross-sectional study as its baseline. (ii) There are currently two large prospective cohort studies in Germany in the recruitment phase, the National Cohort and the Hamburg City Health study.⁴⁰ These studies plan to recruit 200,000 and 45,000 individuals, respectively. Since the response has been found to be similar in resettlers and autochthone Germans, we expect approximately 2% of the study populations to be resettlers, i.e. approximately 5,000 individuals.⁴¹ This sample will allow a detailed assessment of lifestyle, environmental and genetic/epigenetic factors on their mortality and morbidity pattern.

Collaboration

Data of the AMOR studies are not open access, but we encourage other researchers to contact us and apply for data access based on collaborating projects. Please, contact Prof. Dr. Heiko Becher (h.becher@uke.de) or PD Dr. Volker Winkler (v.winkler@uni-heidelberg.de) to apply for possible collaborations.

Further details

Funding declaration

Funding from the German Research Foundation (DFG) and the German Cancer Aid is gratefully acknowledged.

Competing interests

The authors state no competing interests.

Data sharing statement

We welcome collaboration and the data will be shared with investigators. External researchers can get access to the AMOR data through collaborating projects. Please contact the principal investigators and coordinators of the study Prof. Dr. Heiko Becher (h.becher@uke.de) or PD Dr. Volker Winkler (v.winkler@uni-heidelberg.de).

Contributorship statement

VW wrote the manuscript, collected part of the data and is co-PI of the study. SK, AD and VL collected parts of the data and contributed to writing of the manuscript. BH and CM enabled part of the record linkage procedures, helped with data collection and gave critical feedback to manuscript. OR and HB initiated the study and significantly contributed to writing. HB is the PI of the study.

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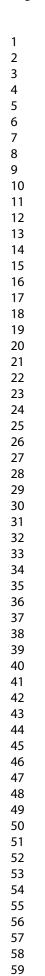
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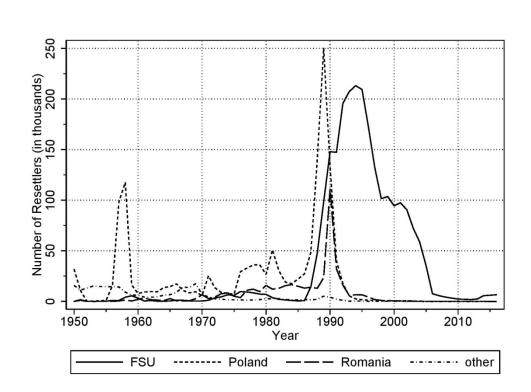
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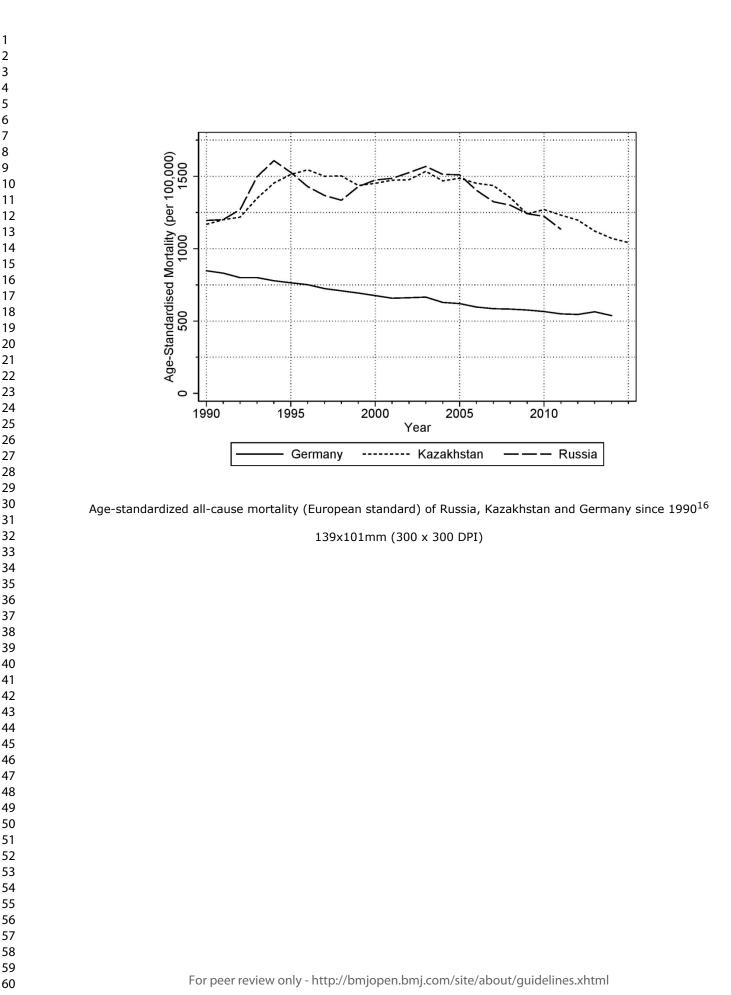


Immigration of resettlers between 1950 and 2016 by country of origin¹¹

139x101mm (300 x 300 DPI)

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	manuscript page / comment
Title and abstract	1	(a) Indicate the study's design with a commonly used term	1
		in the title or the abstract	
		(<i>b</i>) Provide in the abstract an informative and balanced	2
		summary of what was done and what was found	
Introduction			
Background/rational	2	Explain the scientific background and rationale for the	4-6
e		investigation being reported	-
Objectives	3	State specific objectives, including any prespecified	6
	_	hypotheses	-
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates,	7,8
Setting	5	including periods of recruitment, exposure, follow-up, and	7,0
		data collection	
Participanta	6	(<i>a</i>) Give the eligibility criteria, and the sources and	7,8
Participants	6	(<i>a</i>) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of	/,ð
		follow-up	
			not applicable
		(b) For matched studies, give matching criteria and number	not applicable
Variables	7	of exposed and unexposed	7-9
variables	/	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give	/-9
	0*	diagnostic criteria, if applicable	0.10
Data sources/	8*	For each variable of interest, give sources of data and	9,10
measurement		details of methods of assessment (measurement). Describe	
		comparability of assessment methods if there is more than	
Diag	0	one group	0 10 11
Bias	9	Describe any efforts to address potential sources of bias	8,10,11
Study size	10	Explain how the study size was arrived at	7-9
Quantitative	11	Explain how quantitative variables were handled in the	12 (limited because
variables		analyses. If applicable, describe which groupings were	cohort profile)
	10	chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to	12 (limited because
		control for confounding	cohort profile)
		(b) Describe any methods used to examine subgroups and	12 (limited because
		interactions	cohort profile)
		(c) Explain how missing data were addressed	(limited because cohor profile)
		(<i>d</i>) If applicable, explain how loss to follow-up was	-
		addressed	
		(\underline{e}) Describe any sensitivity analyses	(not reported because
			cohort profile)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—	8, 10
		eg numbers potentially eligible, examined for eligibility,	

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		confirmed eligible, included in the study, completing	
		follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	tables 2, 3
Descriptive data	14*	(a) Give characteristics of study participants (eg	table 1
-		demographic, clinical, social) and information on	
		exposures and potential confounders	
		(b) Indicate number of participants with missing data for	table 2
		each variable of interest	
		(c) Summarise follow-up time (eg, average and total	table 2
		amount)	
Outcome data	15*	Report numbers of outcome events or summary measures	12
		over time	
Main results	16	(a) Give unadjusted estimates and, if applicable,	12, table 4
		confounder-adjusted estimates and their precision (eg, 95%	
		confidence interval). Make clear which confounders were	
		adjusted for and why they were included	
		(b) Report category boundaries when continuous variables	-
		were categorized	
		(c) If relevant, consider translating estimates of relative	-
		risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and	11, 12 (limited because
		interactions, and sensitivity analyses	cohort profile)
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 12 (limited because
			cohort profile)
Limitations	19	Discuss limitations of the study, taking into account	13
		sources of potential bias or imprecision. Discuss both	
		direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering	11, 12 (limited because
-		objectives, limitations, multiplicity of analyses, results	cohort profile)
		from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study	13
		results	
Other information			
Funding	22	Give the source of funding and the role of the funders for	13
c .		the present study and, if applicable, for the original study	
		on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.