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RESEARCH ARTICLE

High incidence of dementia in Faroese-born female residents in Denmark

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Abstract

Introduction: To assess whether the incidence of dementia among immigrants in Denmark from the Faroe Islands is similar to that of the inhabitants of their new country.

Methods: Data on Faroese-born immigrants in Denmark were retrieved from the Danish Central Population Register. Incident dementia cases were identified from the Danish National Patient Register. Standardized incidence ratios (SIRs) were used to compare the dementia incidence in immigrants with the general Danish population.

Results: Female, first-generation Faroese immigrants had double the risk of dementia compared with Danes (SIR 2.1, 95% confidence interval [CI] 1.8-2.5); the excess risk prevailed even beyond 10 years in Denmark, and it affected all sub-types of dementia. In male immigrants, only a modest, statistically non-significant excess risk was seen (SIR 1.2, 95% CI 0.9-1.6).

Discussion: The observation of an excess risk of dementia in women only but not in men of Faroese origin living in Denmark underscores the complexity of the etiology of dementia.

KEYWORDS

dementia, Faroe Islands, genetic etiology, immigrants, sex difference

1 | BACKGROUND

The etiology of dementia is unclear; it is considered a complex multifactorial, heterogeneous disease attributable to several inter-related and interacting genetic and environmental factors.¹ Older age, apolipoprotein E (APOE) ϵ 4 allele, and family history of dementia are all consistent but non-modifiable risk factors, for example, Alzheimer's disease (AD), the most prevalent dementia disease.² Other environmental modifiable risk and preventive factors have also been suggested, including cognitive reserve (higher education and IQ), cardiovascular risk factors (hypertension, cholesterol, diabetes, and obesity), and lifestyle and psychosocial factors (depression, smoking, physical activity, and alcohol consumption),^{2,3} albeit few of these

risk factors are known to be causally associated with the risk of dementia.

Studies of health in migrants is an often-used tool to separate the impact of genetics from the impact of environment on health, as migrants keep their genes but change environment. The Faroe Islands are a self-governing nation within the Kingdom of Denmark, and many Faroese move to Denmark for education and employment. In 2014, a total of 48,617 persons lived in the Faroe Islands,⁴ whereas 11,500 persons of Faroese origin lived in Denmark.⁵ We have shown previously that after at least 10 years in Denmark, Faroese immigrants had a higher incidence of Parkinson disease than Danes.⁶ On the contrary, during the first 10 years of their stay in Denmark, Faroese immigrants had a higher incidence of inflammatory bowel diseases (IBDs)

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than Danes, but after 10 years in the new country, their incidence had approached that of the Danes.⁷ The change of environment thus seems to affect the risk of these two diseases very differently.

As dementia is another disease for which both genetic and environmental factors may be part of the etiology, we expected from a study of migrants to learn more about the impact of a new environment on the risk of dementia. We undertook therefore a population-based cohort study of dementia incidence of Faroese immigrants in Denmark.

2 | MATERIAL AND METHODS

2.1 | Study population

The Faroe Islands are located between Iceland and Norway, 1400 km from Denmark. A hereditary predisposition for dementia may exist in this genetically homogeneous and isolated Faroese population, where some genetically inherited diseases occur, such as glycogen storage disease type IIIA,⁸ carnitine transporter deficiency,⁹ and mitochondrial encephalomyopathy,¹⁰ the latter of which may predispose for dementia.

Otherwise, the Faroese and Danish populations are similar in many aspects (Table 1). Life expectancy is high, but somewhat longer in the Faroe Islands than in Denmark, especially for women.¹¹ Fertility is higher in Faroese women than in Danish women.¹¹ Level of education is similar¹¹; the rate of smoking is slightly higher in the Faroe Islands than in Denmark,¹² while alcohol consumption is higher in Denmark than in the Faroe Islands.¹³

In this population-based cohort study, data were retrieved from the Danish Central Population Register (CPR). The CPR includes information on country of birth, and for immigrants, country of emigration and immigration date for every person who ever lived in Denmark since the start of CPR in 1968. Vital status and migration data are updated daily in the CPR, and the unique 10-digit Civil Personal Register numbers enable linkage to other Danish registers.¹⁴

We retrieved data on all Faroese-born residents in Denmark between January 1, 1980 and December 31, 2014. A Faroese immigrant was defined as having the Faroe Islands as the country of birth and/or the Faroe Islands being the country of emigration.

For each person, information on sex, date of birth, dates of immigration(s) and emigration(s), and date of death was retrieved. Person years (pys) were accumulated from January 1, 1980, or from date of first immigration to Denmark, whichever came last; until date of emigration, death, diagnosis of dementia, or December 31, 2014, whichever came first. Re-immigration was frequent and a given person could therefore accumulate pys in more than one risk period; but a given person accumulated pys only for the time he/she actually lived in Denmark. For the entire Danish population, the pys for each calendar year were calculated using the number of inhabitants in the middle of the calendar year. Population data for the Danish population were available from Statistics Denmark.

Diagnoses of dementia are recorded in the Danish National Patient Register founded in 1977, and including information from hospitals

RESEARCH IN CONTEXT

1. Systematic review: There are few studies looking at the incidence of dementia of immigrant groups compared with that of the inhabitants of their new country. The literature review identified only one study, a Swedish register study of incidence of dementia among immigrants.
2. Interpretation: Our findings are in line with those of the Swedish study. We found that the risk of dementia in Faroese women moving to Denmark was double that in Danish women and prevailed even after long-term residence in Denmark. It is noteworthy that in both studies, using similar methodology, an overall excess risk of dementia was observed in female but not in male immigrants from other Nordic countries.
3. Future directions: The observation of an excess risk of dementia in women but not in men of Faroese origin living in Denmark underscores the complexity of the etiology of dementia.

on all inpatients in somatic wards, and since 1995 also all psychiatric inpatient, psychiatric, and somatic outpatient, and emergency department contacts.^{15,16} The International Classification of Diseases, 8th Revision (ICD-8) was used until 1994, when it was replaced by the 10th Revision (ICD-10).¹⁴ For dementia, the following codes were used (ICD-8, ICD10): AD (290.10, F00.0-00.9, G30.0-30.9), Vascular dementia (293.09, 293.19, F01.0-01.9), Frontotemporal dementia (290.11, F02.0), Dementia without specification (290.09, 290.19, F03.9, G31.9), and Other dementias (G31.8). A person became a case on the first date within his/her risk period(s) that he/she was registered with the dementia diagnosis. Because our focus was the risk of dementia, we studied the incidence and not the prevalence of the disease, and to avoid inclusion of prevalent cases, we excluded persons already known with a dementia diagnosis in the patient register prior to 1980.

2.2 | Statistical analysis

Standardized incidence ratios (SIRs) were calculated as the observed number of dementia cases in a given immigrant group divided by the expected numbers calculated from the accumulated pys and the incidence rate for dementia in the Danish population. Standard rates for the Danish population were calculated by sex, 5-year age groups, and 5-year calendar periods. Furthermore, SIRs for Faroese immigrants were calculated by time living in Denmark divided into <10 years and ≥10 years. It should be noted though that the CPR data were left censored to 1980. This means that there will be a certain degree of misclassification on this variable, because some persons can have immigrated to Denmark prior to 1980. It would not have helped to restrict the analysis to persons with a record of immigration after January 1, 1980, because these persons could easily have lived in Denmark also in one or more

TABLE 1 Selected indicators of lifestyle in the Faroe Islands and Denmark around the year 2000

	Men		Women		Overall		Year	Reference
	FO	DK	FO	DK	FO	DK		
Latitude degree, °C			-	-	62	55-57	-	
Ethnic origin			-		White		-	
Life expectancy, years	76.1	74.5	81.3	79.2			2000	11
Fertility per 1000 women	-	-	2581.9	1771.5			2000	11
Highest achieved education ^b , %							2006	11
Primary school	30	35	36	37				
Secondary	45	44	43	38				
Tertiary	25	21	21	25				
Daily smokers, 15 years or older, %	38	31	35	26			2001	13
Alcohol, liter per person ^a					6.8 ^a	11.5 ^a	2000	12

^aFor men and women in total.

^b15 to 74 years.

[#]Not consumed in Denmark.

period(s) prior to 1980. Sensitivity analyses were performed excluding the incident cases that had been living in Denmark for <2 years (Supplementary Table 1). The 95% confidence intervals (CIs) for SIRs were calculated using the square-root transform.

2.3 | Ethics

This is a register-based research project with no contact with patients, their relatives, or treating physicians. The Danish Data Protection Agency approved the study, journal no: 2014-41-3538. Data from CPR and the Danish National Patient Register were obtainable via Statistics Denmark.

3 | RESULTS

The cohort included 57,373 persons of Faroese origin contributing 812,196 pys. In first-generation immigrants a total of 324 680 pys were accumulated, of which 19% were in persons 60 years of age or older (Table 2).

In total, 228 incident all-cause dementia cases were observed in first-generation immigrants (Table 3). For first-generation immigrants, the SIR was 1.8 (95% CI 1.6-2.1); 1.6 (95% CI 1.1-2.2) during the first 10 years in Denmark and 1.9 (95% CI 1.6-2.2) for stays beyond 10 years. The excess risk derived primarily from women for whom the SIR was 2.1 (95% CI 1.8-2.5), whereas the excess was more modest and statistically non-significant in men: SIR 1.2 (95% CI 0.9-1.6). Of note, two thirds of pys were accumulated by migrants with only one period in Denmark, that is, not immigrating back and forth, whereas the majority (94%) of cases with all-cause dementia had only one period in Denmark.

Of the 228 all-cause dementia, 92 cases with AD were observed in first-generation immigrants (Table 4). For first-generation immigrants, the SIR was 2.1 (95% CI 1.7-2.6); 1.7 (95% CI 0.6-3.8) during the first 10 years in Denmark, and 2.1 (95% CI 1.7-2.6) for stays beyond 10

TABLE 2 Characteristics of first-generation immigrants from the Faroe Islands in Denmark by sex, year of birth, and year of first immigration to Denmark

Year of birth (persons)	First-generation		
	Men (n)	Women (n)	Total (n)
<1949	2075	3291	5366
1950-1959	1441	1660	3101
1960-1969	2143	2328	4471
1970-1979	2228	2557	4785
1980-1989	2144	2450	4594
≥1990	1861	2230	4091
All persons	11892	14516	26408
Current period (pys)			
1980-1989	27047.7	41758.7	68806.4
1990-1999	40322.7	56223.9	96546.6
2000-1909	41926.6	60029.1	101956
2010-2014	23940.4	33431.0	57371.4
Current age (pys)			
0-19	22291.2	24304.4	46595.5
20-29	30234.3	41132.0	71366.3
30-39	25359.5	33028.8	58388.2
40-49	19244.0	28825.2	48069.2
50-59	15270.0	24133.0	39403.0
60-69	11447.6	19450.4	30897.9
70-79	6630.4	13203.4	19833.7
80+	2760.5	7365.7	10126.2

Person years (pys) for the same groups by calendar period and age.

years. The excess risk derived primarily from women for whom the SIR was 2.5 (95% CI 2.0-3.1), whereas the excess was more modest and statistically non-significant in men: SIR 1.2 (95% CI 0.7-1.9). Furthermore, in the first-generation, 141 had dementia without specification and 25 and vascular dementia. The SIRs for these diagnosis showed the

TABLE 3 Standardized incidence ratio (SIR)^a of all cause dementia for first-generation immigrants from the Faroe Islands in Denmark

	All			Men			Women					
	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)
First generation	325114	228	123.929	1.8 [1.6-2.1]	133570	51	41.14	1.2	191544	177	82.78	2.1
First generation <10 years in DK	172270	37	23.52	1.6 [1.1-2.2]	74816	7	7.74	0.90	97454	30	15.78	1.9 [1.3-2.7]
First generation >10 years in DK	152921	191	100.78	1.9 [1.6-2.2]	58776	44	33.55	1.3 [1.0-1.8]	94145	147	67.23	2.2 [1.9-2.6]

Bold numbers indicate significance at 0.05 level.

Abbreviation: DK = Denmark. Dementia includes: Alzheimer's disease, Vascular dementia, Frontotemporal dementia, Dementia without specifications, Other dementias.

^aStandardized incidence ratios (SIRs) were calculated as the observed number of dementia in the Faroese immigrant group divided by the expected numbers calculated from the accumulated person-years (pys) and the incidence rate for dementia in the Danish population. Standard rates for the Danish population were calculated by sex, 5-year age groups, and 5-year calendar periods.

TABLE 4 Standardized incidence ratio (SIR)^a of Alzheimer's disease for first-generation immigrants from the Faroe Islands in Denmark

	All			Men			Women					
	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)
First generation	325724	92	43.68	2.1 [1.7-2.6]	133725	16	13.45	1.2	191999	76	30.23	2.5 [2.0-3.1]
First generation: <10 years in DK	172357	6	3.48	1.7 [0.6-3.8]	74842	0	1.29	0	97515	6	2.19	2.7 [1.0-6.0]
First generation: >10 years in DK	153338	86	40.21	2.1 [1.7-2.6]	58869	16	12.16	1.3	94469	70	28.04	2.5 [2.0-3.2]

Bold numbers indicate significance at 0.05 level. DK = Denmark; Alzheimer's disease: ICD-8 = 290.10, ICD-10 = F00.0-00.9, and ICD-10 = G30.0-30.9.

^aStandardized incidence ratios (SIRs) were calculated as the observed number of dementia in the Faroese immigrant group divided by the expected numbers calculated from the accumulated pys and the incidence rate for dementia in the Danish population. Standard rates for the Danish population were calculated by sex, 5-year age groups, and 5-year calendar periods.

same tendencies, with higher risks among Faroese immigrants primarily derived from women (Tables 5 and 6).

Repeating the analyses excluding incidence cases that had moved to Denmark <2 years prior to the diagnosis changed the SIRs only marginally (Supplementary Table 1).

4 | DISCUSSION

Based on nationwide data we found that the risk of dementia in Faroese women moving to Denmark was double that in Danish women. This excess risk was found for all subtypes of dementia, and it prevailed even after long-term residence in Denmark. Faroese men moving to Denmark had the same risk of dementia as Danish men during their first 10 years in Denmark, while they had a slight excess risk after long-term residence in Denmark.

Diagnosing and managing dementia in migrants may pose challenges as illustrated for instance for elderly men of Turkish, Pakistani, and ex-Yugoslavian origin in Denmark.¹⁷ However, Faroese immigrants in Denmark likely do not experience great barriers, as the countries and their health care systems are quite similar. The excess dementia risk in women of Faroese origin is unlikely to be explained by differences in access to health care and/or differences in services provided in health care, although there still may be differences in health-seeking behaviors in immigrant versus native-born populations.¹⁸ In addition, the communication barriers may occur as Danish is not the first language. However, the two languages are related and Danish is mandatory in school from third grade and all Faroese inhabitants speak Danish. Language is therefore less likely to have influenced performance on cognitive testing differentially between Faroese immigrants and Danes. Good social support in daily life most likely can postpone a dementia diagnosis,¹⁹ and one could anticipate that a limited social network and consequently more stress in daily life could explain the excess risk of dementia in women of Faroese origin in Denmark. It should be noted, however, that we have no data to support this hypothesis.

A Swedish register study, which to our knowledge is the only other study of incidence of dementia among immigrants, included >3 million people aged ≥45, and diagnoses recorded in the Swedish National Patient Register. Overall, male immigrants from the Nordic countries had the same incidence of dementia as Swedes (hazard ratio [HR] 1.02, 95% CI 0.98-1.06), but the risk was increased for Finnish immigrants (HR 1.4, 95% CI 1.08-1.20). Female immigrants from the Nordic countries had an increased risk of dementia (HR 1.11, 95% CI 1.08-1.15), deriving from Finnish (HR 1.20, 95% CI 1.15-1.24), and Norwegian (HR 1.14, 95% CI 1.07-1.22) immigrants, whereas decreased rates were seen for both Danish and Icelandic immigrants.²⁰ The methodology of the Swedish study is similar to the one used in our study, and it is noteworthy that in both studies an overall excess risk of dementia was observed in female but not in male immigrants from other Nordic countries.

Another study compared the prevalence of dementia and memory impairment in 2008 in the Norwegian Primary Health Care Register between immigrants and Norwegians. Immigrants from high-income

TABLE 5 Standardized incidence ratio (SIR)^a of dementia without specification for first-generation immigrants from the Faroe Islands to Denmark

	All			Men			Women					
	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)
	First generation	325475	141	79.13	1.8 [1.5-2.1]	133643	34	25.82	1.3 [0.9-1.8]	191833	107	53.30
First generation: <10 years in DK	172283	32	19.99	1.6 [1.1-2.3]	74817	6	6.28	1.0 [0.3-2.1]	97467	26	13.71	1.9 [1.2-2.8]
First generation: > 10 years in DK	153264	109	59.38	1.8 [1.5-2.2]	58846	28	19.63	1.5 [1.0-2.1]	94417	81	39.75	2.0 [1.6-2.5]

Bold numbers indicate significance at 0.05 level. DK = Denmark; Dementia without specification: ICD-8 = 290.09 and 290.19, ICD-10 = F03.9 and G31.9.

^aStandardized incidence ratios (SIRs) were calculated as the observed number of dementia in the Faroese immigrant group divided by the expected numbers calculated from the accumulated person-years and the incidence rate for dementia in the Danish population. Standard rates for the Danish population were calculated by sex, 5-year age groups, and 5-year calendar periods.

TABLE 6 Standardized incidence ratio (SIR)^a of vascular dementia for first-generation immigrants from the Faroe Islands in Denmark

	All			Men			Women					
	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)	Person-years	Observed	Expected	SIR (95% CI)
First generation	325969	25	14.05	1.8 [1.2-2.6]	133772	4	5.60	0.7 [0.2-1.8]	192197	21	8.45	2.5 [1.5-3.8]
First generation: <10 years in DK	172360	5	1.88	2.7 [0.8-6.3]	74842	1	0.77	1.3 [0.0-7.4]	97518	4	1.11	3.6 [0.9-9.4]
First generation: >10 years in DK	153581	20	12.18	1.6 [1.0-2.5]	58917	3	4.83	0.6 [0.1-1.9]	94664	17	7.35	2.3 [1.3-3.7]

Bold numbers indicate significance at 0.05 level. DK = Denmark; Vascular dementia: ICD-8 = 293.09 and 293.19; ICD-10 = F01.0-01.9.

^aStandardized incidence ratios (SIRs) were calculated as the observed number of dementia in the Faroese immigrant group divided by the expected numbers calculated from the accumulated pys and the incidence rate for dementia in the Danish population. Standard rates for the Danish population were calculated by sex, 5-year age groups, and 5-year calendar periods.

countries had an odds ratio (OR) of 0.90 (95% CI 0.83-0.98) and other immigrants an OR of 0.84 (95% CI 0.73-0.96) for the two conditions. Data were not reported separately for immigrants from Nordic countries.²¹ Because the methodology of this study is quite different from the one used in our study, it is difficult to compare the results.

In a US prospective cohort study, persons with less than high school education were found to have a higher incidence of dementia than persons with at least high school education.²², i.e. in Mexican Americans, education was a significant mediator of the association between age at migration and cognitive impairment.²² It is unlikely, however, that the excess risk of dementia in women of Faroese origin in Denmark could be mediated by education, as many of these women presumably moved to Denmark primarily to obtain an education, and on this background they are expected on average to have a similar level of education as Danes. Of note, neither non-native language use²³ nor bilingualism²⁴ has been found to protect against dementia.

Based on the Danish National Patient Register and the Psychiatric Central Research Register the age-standardized (European Union) incidence rate of dementia for persons older than 65 years was 10.46 per 1000 pys in 2003, with slightly higher rates for women than for men.²⁵ Based on Faroese hospital data registration using strict diagnostic criteria, the age-standardized (Western European population) rate of dementia was on average 5.5 per 1000 in 2010-2017, systematically about 30% higher for women than for men.¹² On this basis, one may wonder why female immigrants from the Faroese Islands in Denmark then had an excess risk of dementia in Denmark. It should be taken into account though that calculated incidence rates are highly sensitive to the diagnoses recorded in the registers.

For IBDs, we have shown previously that to mimic the incidence rate based on the strict Copenhagen Diagnostic Criteria, only persons registered two to three times with a diagnosis of IBDs in the National Patient Register should be included.²⁶ On this basis, one should be cautious in comparing the reported incidence rates for dementia in Denmark and the Faroe Islands. It is clear though that women are at a higher risk of dementia in both Denmark²⁵ and the Faroe Islands,²⁷ an observation in accordance with a number of studies that report higher incidence rates of AD in women relative to men, particularly in persons older than age 80 to 85 years.²⁸⁻³¹ However, the results have been inconsistent and other epidemiologic studies did not find a difference in incidence of AD or all types of dementia between the sexes.³²⁻³⁵ Still, irrespective of statistical significance, many studies descriptively suggest sex differences,²⁸ but the mechanisms underlying this proposed sexual divergence are largely unknown.³⁶⁻³⁸

An important strength of the study was that all risk periods could be measured accurately due to the availability of complete immigration and emigration histories in the Danish population register. It was important also that we had many Faroese immigrants staying for at least 10 years in Denmark so we were able to estimate the impact of a long-term stay in the new environment. Almost all of the dementia cases occurred in immigrants who stayed for only one period in Denmark, indicating that the risk was associated with stay in Denmark rather than with the stress from moving back and forth. The validity of the dementia diagnoses in the Danish National Patient Register is

high; a previous study found 85.8% of the dementia diagnoses to be correct.³⁹ The use of Danish National Patient Register data for identification of incident cases both among the immigrants and among the Danes ensured that the same case definitions were used for the numerator and for the denominator. Any possible drift over time in recording of dementia diagnosis will also have affected the observed and the expected numbers of cases in the same way.

The study also has some limitations, however. We defined an incident dementia case as the first time a person had a discharge diagnosis of dementia, and routine discharge diagnoses may be affected by some inaccuracy.⁴⁰ In the analysis, we controlled for sex, age, and calendar year, which means that data from young age groups with few dementia cases will contribute limited information. We were, however, not able to control for other risk such as sociodemographic, social, or physical/mental health risk factors, as these data were not available for this study. Furthermore, different forms of dementia are not easily distinguished using register data. This is a limitation in the part of the present study where we analyzed types of dementia separately.

The pertinent question in the interpretation of immigrant studies is whether the results point to a genetic or an environmental origin of the disease. The diverging results for women and men in the present study make it difficult to answer this question. That the excess risk of dementia in female immigrants was seen from the beginning of their stay in Denmark, and that it prevailed even after a long-term stay in Denmark could point to a sex-linked genetic etiology. However, it might also point to a sex-linked exposure early in life that affected the risk of disease throughout life despite later lifestyle changes. Or it might be that the change from the Faroese to the Danish culture affects women more and earlier than it affects men. The two latter possibilities might point to sex-linked environmental risk factors for dementia. Finally, a possible selection effect should be considered if the predisposition for dementia differed between migrating women and men. The observed excess risk for female immigrants calls for further studies of possible social and psychological determinants, and a longer follow-up will show whether or not the patterns for women and men will converge.

In conclusion, this population-based study showed an excess risk of dementia in Faroese women moving to Denmark. This excess risk prevailed even after a long-term stay in Denmark, and it affected all subtypes of dementia. In contrast, during their first 10 years of stay in Denmark, Faroese men had the same risk of dementia as Danish men, whereas long-term stay was associated with a slightly elevated risk.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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