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SHORT COMMUNICATION

Immigration to Israel during childhood is associated with diabetes at adolescence: a study of 2.7 million adolescents

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Abstract
Aims/hypothesis Immigration studies can shed light on diabetes pathogenesis and risk factors. To this end, we investigated the association between age at immigration and diabetes occurrence at adolescence among immigrants to Israel.
Methods We analysed cross-sectional data on 2,721,767 Jewish adolescents assessed for mandatory military service at approximately 17 years of age between 1967 and 2014. The study population comprised 430,176 immigrants with origins in Ethiopia, former USSR, Middle East and North Africa (ME/NA) and western countries. ORs for diabetes were calculated for men and women, grouped according to age at immigration, with Israel-born participants as controls. Unadjusted and fully adjusted models were made to account for possible confounders. Additionally, the study population was stratified by origin and each immigrant group was referenced to Israel-born participants of the same origin.
Results There was a graded decrease in OR for diabetes across the study groups in the fully adjusted model. Immigrants arriving at age 0–5 years had comparable OR for diabetes to the Israeli-born reference group; those arriving at age 6–11 years had an OR of 0.82 (95% CI 0.70, 0.97; $p = 0.017$) and recent immigrants, arriving at age 12–19 years, had the lowest OR of 0.65 (95% CI 0.54, 0.77; $p < 0.0001$). When age at immigration was treated as a continuous variable, there was an adjusted risk for occurrence of diabetes of 0.97 (95% CI 0.96, 0.99; $p = 0.001$) for every year increment. The lower risk for diabetes among recent immigrants persisted in the unadjusted model and persisted when the study sample was stratified by sex and origin, except for immigrants arriving from ME/NA. Notably, Ethiopians born in Israel had a sixfold higher diabetes crude prevalence than Ethiopian immigrants arriving after the age of 5 years.
Conclusions/interpretation Immigrants of different ethnic groups arriving earlier in childhood lose their protection against diabetes at adolescence, relative to children born in Israel. This is perhaps due to environmental and lifestyle changes, especially those beginning at an early age.

Keywords Adolescent · Childhood · Diabetes mellitus · Environmental exposure · Ethnic groups · Immigration and emigration · Lifestyle · Pathogenesis · Risk factors

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Abbreviations

IDF	Israeli Defense Forces
ME/NA	Middle East and North Africa

Introduction

The incidence of diabetes in childhood and adolescence, with type 1 diabetes accounting for most cases, has increased worldwide in recent decades [1, 2]. In Israel, the increase in annual incidence between 1997 and 2010 among Jews and Arabs was 3.6% and 4%, respectively. This is higher than the 3.2%, 2.8% and 2.3% reported in Denmark, UK and Colorado, respectively, but lower than the 4.7% increase in Finland between 1980 and 2005 [1]. This global rise is mostly attributed to changes in environment and lifestyle which have only been partially identified [3]. Also, a greater influence is often attributed to exposure to environmental risk factors in early life [3]. The study of diverse migrant populations, exposed to changes in environment, nutrition, social structures, stress inducers and physical activity levels following immigration and acculturation, can provide insight into the genetic–environmental–lifestyle interactions underlying disease pathogenesis [4]. Furthermore, such studies can help examine the effects of early and later-life exposures on the risk for diabetes, providing they include immigrants' age at immigration. We know of only one such study, which found that the age at which immigrants and adoptees arrived in Sweden had no significant influence on the risk for type 1 diabetes but did find an increased risk for those born in Sweden to immigrant parents [5]. Other studies that examined the effects of immigration in general on type 1 diabetes risk have shown conflicting results over the years [4, 6].

Israel presents an ideal 'laboratory' for this type of study. It is a developed country that has always been an immigration destination for people from all over the globe. The aim of the present study was to examine the association between age at immigration and occurrence of diabetes among 2.7 million adolescents over the last five decades.

Methods

Study design and population In Israel, all Jewish residents and some minorities are obliged to serve in the Israeli Defense Forces (IDF). As part of the draft process, they go through a medical evaluation at the age of approximately 17 years, including a medical interview, a review of medical history provided by the primary care physician and a physical examination performed by a physician [7]. In addition, sociodemographic data are obtained. The institutional review board of the IDF Medical Corps approved this study.

The study population included all Jewish adolescents, aged 16–19 years, examined at the recruitment centers between 1967 and 2014. This included 2,721,767 examinees of whom 4733 were diagnosed with diabetes (see ESM Fig. 1). The sample was considered nationally representative for Jewish men [7] but less so for Jewish women, as Orthodox women are exempt from military service and are not usually examined. Further details of the study design, setting and population are given in the ESM Methods.

Date of birth and date of immigration were obtained from the Israeli Ministry of Internal Affairs database and the age at immigration was computed accordingly. Age at immigration was categorised as follows: 0–5 years, 6–11 years and 12–19 years. Origin for immigrants was defined by country of birth. Origin for Israeli-born was defined by paternal country of birth (or paternal grandfather's if the father was born in Israel), as described previously [7]. Diabetes cases were based on a physician diagnosis of diabetes according to ADA criteria (see ESM Methods).

Statistical analysis Distribution of all study variables in participants grouped according to age at immigration was performed for the total population. Associations between age at immigration and diabetes were assessed by univariate and multivariable logistic regression models. Finally, the study population was stratified by origin and the fully adjusted model was applied to each immigrant group, with Israel-born participants of the same origin as reference, and with an additional Israeli-native group (at least fourth generation immigrants) for comparison.

ORs are presented with 95% CIs. All tests were two-tailed and statistical significance was defined as $p < 0.05$. Statistical analyses were performed with SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

For more detailed information on study variables and sensitivity analysis preformed, please refer to ESM Methods.

Results

Baseline characteristics of the study population grouped according to age at immigration are shown in Table 1. Mean ± SD age at assessment was 16.9 ± 0.5 years for the Israeli-born group and the group aged 0–5 years at immigration, 17.0 ± 0.6 years for those aged 6–11 years at immigration and 17.5 ± 0.8 years for those aged 12–19 years at immigration. Of the Israeli participants, 84.2% were Israeli-born, whereas only 9.1% were Israeli-native (at least four generations in Israel).

There was a graded decrease in diabetes crude prevalence across the study groups for the total population: 1.87, 1.58 and 1.47 per 1000 for immigrants arriving at age

Table 1 Baseline characteristics of the study population according to age at immigration category

Characteristic	Israeli-born	Age at immigration			Total[a]
		0–5 years	6–11 years	12–19 years	
Total, *N* (%)	2,291,591 (100.0)	158,616 (100.0)	137,799 (100.0)	133,761 (100.0)	2,721,767 (100.0)
No. of diabetes cases, *n* (%)	4023 (100.0)	297 (100.0)	217 (100.0)	196 (100.0)	4733 (100.0)
Age at assessment, years	16.9 ± 0.5	16.9 ± 0.5	17.0 ± 0.6	17.5 ± 0.8	16.9 ± 0.5
Sex					
Men	1,341,668 (58.5)	99,021 (62.4)	86,120 (62.5)	92,984 (69.5)	1,619,793 (59.5)
Women	949,923 (41.5)	59,595 (37.6)	51,679 (37.5)	40,777 (30.5)	1,101,974 (40.5)
Birth year					
1947–1959	315,640 (13.8)	42,926 (27.1)	33,636 (24.4)	26,414 (19.7)	418,616 (15.4)
1960–1979	937,066 (40.9)	44,063 (27.8)	29,778 (21.6)	60,057 (44.9)	1,070,964 (39.3)
1980–1998	1,038,885 (45.3)	71,627 (45.2)	74,385 (54.0)	47,290 (35.4)	1,232,187 (45.3)
Socioeconomic status					
Low	546,396 (24.3)	47,040 (30.7)	41,926 (31.4)	38,052 (29.4)	673,414 (25.3)
Mid	1,159,615 (51.6)	81,676 (53.2)	74,882 (56.1)	74,072 (57.2)	1,390,245 (52.2)
High	541,662 (24.1)	24,714 (16.1)	16,583 (12.4)	17,338 (13.4)	600,297 (22.5)
Origin					
Israel	207,673 (9.3)	2169 (1.4)	335 (0.2)	266 (0.2)	210,443 (7.9)
Former USSR	158,756 (7.1)	58,495 (36.5)	74,335 (53.9)	87,449 (65.4)	379,035 (14.2)
ME/NA	1,157,522 (51.9)	48,316 (30.1)	26,361 (19.1)	14,340 (10.7)	1,246,539 (46.8)
Western countries	691,095 (31.0)	42,617 (26.6)	28,074 (20.4)	25,528 (19.1)	787,314 (29.6)
Ethiopia	13,889 (0.6)	8786 (5.5)	8802 (6.4)	6082 (4.6)	37,559 (1.4)

Categorical variables are presented as number (% of total). Age at assessment is given as a continuous variable as mean ± SD

[a] Numbers do not always add up to 2,721,767 due to missing information regarding origin and socioeconomic status

0–5, 6–11 and 12–19 years, respectively (Table 2). This pattern retained logistic regression analysis, regardless of model used.

In univariable analysis, OR for diabetes was 0.83 (95% CI 0.72, 0.96) among recent immigrants compared with the Israeli-born population and became more pronounced in the fully adjusted model (OR 0.65; 95% CI 0.54, 0.77). In the univariable model, immigrants arriving at age 0–5 years and 6–11 years had comparable odds for occurrence of diabetes compared with the Israeli-born population. However, in the fully adjusted model, immigrants arriving at age 6–11 years had an OR of 0.82 for diabetes (95% CI 0.70, 0.97). When age at immigration was treated as a continuous variable, there was an adjusted risk for occurrence of diabetes of 0.97 (95% CI 0.96, 0.99) for every year increment.

The lower risk for diabetes occurrence among recent immigrants persisted when the study sample was stratified by sex (ESM Tables 1,2) and origin except in immigrants from the Middle East and North Africa (ME/NA). Ethiopian immigrants arriving at all age groups demonstrated lower odds for diabetes compared with Israeli-born Ethiopians who had a 4.46 per 1000 crude prevalence for diabetes, the highest among all groups, sixfold higher than Ethiopian immigrants arriving after the age of 5 years.

Discussion

In this vast retrospective study of 2.7 million Jewish adolescents we found an association between immigration at an older age and lower frequency of diabetes at adolescence, compared with the Israeli-born population. The findings were emphasised following adjustment for potential confounders and when the study sample was stratified by sex and origin.

The observed association may be linked to two mechanisms, acting together or apart. The first, longer duration of stay in an industrialised country such as Israel, especially for immigrants arriving at young ages, plays a key role in altering diabetes risk by means of higher lifestyle acculturation. Correlating with this notion is the beta cell stress hypothesis. This proposes a mechanism by which all factors that increase insulin demand or resistance, such as overweight, sedentary lifestyle, rapid growth, psychological stress and glucose overload, may be crucial in type 1 diabetes development [3, 8]. Supporting this hypothesis are the rising rates of adolescent overweight and obesity in Israel over the last decades [9]. Moreover, former research by Meydan et al [10] on a portion of our study population found greater risk for being overweight or obese at age 17 years among USSR and Ethiopian immigrants arriving in Israel at early ages. They

Table 2 ORs for diabetes across age at immigration categories for the total population and different origins

Origin/analysis	Israeli-born[a]	Age at immigration			Israeli-native
		0–5 years	6–11 years	12–19 years	
Total population					
N	2,291,591	158,616	137,799	133,761	–
Diabetes cases, *n*	4023	297	217	196	–
Prevalence per 1000	1.76	1.87	1.58	1.47	–
Unadjusted model					
OR (95% CI)	1.00	1.07 (0.95, 1.20)	0.90 (0.78, 1.03)	0.83 (0.72, 0.96)	–
p value	–	0.283	0.119	0.013	–
Fully adjusted model[b]					
OR (95% CI)	1.00	0.99 (0.87, 1.14)	0.82 (0.70, 0.97)	0.65 (0.54, 0.77)	–
p value	–	0.898	0.017	<0.0001	–
Ethiopia					
N	13,889	8786	8802	6082	207,673
Diabetes cases, *n*	62	16	5	6	419
Prevalence per 1000	4.46	1.82	0.57	0.99	2.02
Fully adjusted model					
OR (95% CI)	1.00	0.43 (0.25, 0.74)	0.14 (0.05, 0.34)	0.20 (0.09, 0.48)	0.63 (0.48, 0.83)
p value	–	0.003	< 0.0001	< 0.0001	0.001
Western countries					
N	691,095	42,617	28,074	25,528	207,673
Diabetes cases, *n*	1247	84	40	28	419
Prevalence per 1000	1.80	1.97	1.41	1.10	2.02
Fully adjusted model					
OR (95% CI)	1.00	1.04 (0.82, 1.31)	0.80 (0.56, 1.14)	0.38 (0.25, 0.59)	0.71 (0.63, 0.79)
p value	–	0.749	0.212	< 0.0001	< 0.0001
Former USSR					
N	158,756	58,495	74,335	87,449	207,673
Diabetes cases, *n*	319	173	157	150	419
Prevalence per 1000	2.01	2.96	2.11	1.72	2.02
Fully adjusted model					
OR (95% CI)	1.00	1.13 (0.94, 1.37)	0.98 (0.81, 1.19)	0.80 (0.65, 0.99)	0.83 (0.71, 0.96)
p value	–	0.189	0.854	0.043	0.013
ME/NA					
N	1,157,522	48,316	26,361	14,340	207,673
Diabetes cases, *n*	1393	17	13	7	419
Prevalence per 1000	1.20	0.35	0.49	0.49	2.02
Fully adjusted model					
OR (95% CI)	1.00	0.71 (0.38, 1.33)	0.78 (0.35, 1.75)	0.44 (0.140, 1.37)	1.11 (0.99, 1.25)
p value	–	0.281	0.546	0.154	0.064

[a] Reference group for the different origins is Israeli-born of same origin

[b] Fully adjusted model: adjusted for birth year, age at assessment, sex, origin and residential socioeconomic status. Input from 99,659 subjects (including 663 diabetes cases) is missing in this model due to lack of sociodemographic data (origin, socioeconomic status, or both)

suggested that their findings were linked to lengthier stay in Israel or to greater influence of the environmental switch during physiological changes occurring in early childhood. Regarding glucose overload, total sugar intake is associated with an increased risk of progression to type 1 diabetes in children with islet autoimmunity, and sugar-sweetened beverages may be especially detrimental to children with high-risk *HLA-DR/DQ* genotype [8]. Such is the case for Ethiopian immigrants in Israel; this population, apart from integrating high-sugar foods (including sweetened beverages) into their diet [10], was found by Zung et al [11] to have a remarkably high prevalence of the highly susceptible allele *DRB1*03:01* (25.2%). Researchers also noted high diabetes incidence rates and lower age at diagnosis for Ethiopian individuals with two susceptible haplotypes and longer duration of stay of their family in Israel prior to birth, and assumed this was due to a higher degree of acculturation. These findings, as well as our observation in which Ethiopians born in Israel have the highest prevalence of diabetes, by far, are especially striking when compared with the low incidence rates recently reported in the rural Gondar region of Ethiopia, from where most Jewish Ethiopian immigrants originated [12].

Another hypothesis is that immigrants arriving at younger ages are more susceptible to diabetogenic triggers brought on by their new environment. Exposure to cows' milk, toxins, viral infections and psychological stress are thought to have more effect during early life [3]. On this subject, an intriguing study found that parental psychological stress, foreign maternal origin and serious life events during a child's first year of life were all associated with the development of islet autoimmunity at the age of 12 months [13].

This study has several limitations. First, as this is a cross-sectional study, we cannot infer causality. For instance, a possible explanation for the low risk found among older immigrants is that children with diabetes and their families are perhaps less likely to migrate to another country. Second, we could not distinguish between the different types of diabetes in our database; hence, our results encompass all types of diabetes but are probably more linked to type 1 [2]. Third, we could not adjust for potential confounders, such as breast feeding, family history and day care, as data were not available.

Strengths of this study include its large sample size, stratification for sex and origin and adjustment for variables such as birth year, origin, sex and socioeconomic status.

In conclusion, we found an increase in OR for diabetes among adolescent immigrants with earlier ages of arrival into Israel. Prevention programmes are needed, at least for the very-high-risk groups, such as Israeli-born Ethiopians and young Ethiopian immigrants, beginning shortly after their arrival and focusing on nutritional and physical activity habits. Further studies are warranted to validate this association and identify the lifestyle and environmental factors linked to it.

Data availability The datasets analysed during the current study are not publicly available due to IDF restrictions.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement AP, BG, GT, AA and ED contributed to the conception and design of the study. AP and BG contributed to acquisition, analysis and interpretation of data. ED contributed to acquisition of data and performed statistical analysis. GT, AA, JM, IR and ML contributed to interpretation of data. AP and BG drafted the manuscript and GT, AA, JM, IR, ML and ED critically revised it for important intellectual content. All authors provided final approval of the version to be published. BG and AA are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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