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Maternal and Childhood Diet and Human Type 1 Diabetes Risk

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Abstract

Background: The incidence of type 1 diabetes is increasing worldwide for reasons which are incompletely understood. The objective of the study was to investigate the potential association of maternal and childhood dietary components to type 1 diabetes in a case-control retrospective study.

Methods: Data of diet during pregnancy and during childhood before the diagnosis of type 1 diabetes were gathered using a modified food frequency questionnaire in 88 mothers of type 1 diabetes patients and 88 mothers of controls. Children born on the same day and of the same sex of type 1 diabetes patients were chosen as controls.

Results: Consumption of savoury cakes, savoury pies and ice-cream was significantly more frequent in mothers of type 1 diabetic subjects than in mothers of controls in univariate, but not in multivariate, analysis. Children with type 1 diabetes consumed bread and fish more frequently, and chicken less frequently before diagnosis when compared to controls. There were no differences in the frequency of intake of milk, sweet drinks and tea, fruit, dried fruit, vegetables, potatoes, uncooked cereal, rice or pasta, pizza, savoury cakes and pies, biscuits, packaged snacks, cakes, candy or chocolate. Consumption of bread was independently associated with increased risk of type 1 diabetes whilst consumption of chicken was independently associated with decreased risk in multivariate analysis.

Conclusion: We support the hypothesis that dietary factors may be implicated in the pathogenesis of type 1 diabetes.

Keywords: Type 1 diabetes; Childhood diet; Maternal diet; Pathogenesis

Introduction

In spite of advances in therapy, type 1 diabetes is still associated with a number of long-term complications and with decreased health-related quality of life [1]. It is also associated with reduced life expectancy [2, 3]. Very recently, Heald et al reported that type 1 diabetes results in an average of 7.6 years of life lost [2], whilst Livingstone et al reported that it is associated with approximately 11 years of life lost for men and 13 years for women [3]. Type 1 diabetes also has significant societal costs, including loss of work days [1] and health care related costs [4].

The incidence of type 1 diabetes is increasing worldwide [5], with over 1.1 million persons under 20 years of age currently living with type 1 diabetes globally [5]. It has also been reported that the contribution of genetic factors has decreased over time [6]. Both these observations suggest that environmental factors are becoming more increasingly important. Type 1 diabetes is known to have a long preclinical phase [7, 8], so that environmental factors in the years before diagnosis of type 1 diabetes may be potentially important. Dietary factors have been proposed as one potential mechanism [9]. Dietary factors have profound effects on the gut microbiome [10, 11], which is thought to play an important role in the pathogenesis of type 1 diabetes [12]. Dietary factors in childhood can also induce islet cell autoimmunity [13, 14], possibly mediated by microbiome changes [15, 16]. Maternal diet may also modulate the child's microbiome [17]. In an animal model, maternal gluten-free diet has been reported to protect against type 1 diabetes [18, 19]. However, human studies have been more inconclusive [20, 21].

The aim of the present study was therefore to investigate the potential association of maternal and childhood dietary components to type 1 diabetes in the child. We used a case-control retrospective design since randomized controlled studies are difficult to conduct in this subject area. Furthermore, participation in a dietary intervention study may have an impact on overall nutrient and food intake quality [22]. We chose to investigate those dietary constituents which are commonly consumed in Malta.

Materials and Methods

In this retrospective case-control study, mothers of patients of Maltese descent diagnosed with type 1 diabetes were invited to participate as cases. Patients were identified and randomly selected from a national database of subjects with entitlement to type 1 diabetes treatment. The diagnosis of type 1 diabetes was confirmed through examination of health records. Type 1 dia-

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betes was defined as having had a history of unprovoked diabetic ketoacidosis and/or positive antibodies to islet cell and/or glutamic acid decarboxylase and/or to insulin. For each child with type 1, a child born on the same day and of the same sex, as identified from the national birth register, was randomly selected as a control. Exclusion criteria included type 2 diabetes or presence of other autoimmune conditions. The study was carried out between November 2019 and August 2020.

Data collection of maternal and childhood diet was performed using a modified food frequency questionnaire (FFQ) [23]. The mothers completed the FFQ with regard to their diet during the pregnancy of interest and the FFQ on the diet of the child up to the age of diagnosis of type 1 diabetes. Mothers were asked about their diet during the pregnancy of the child who eventually developed type 1 diabetes or of the respective controls. Maternal diet assessed was the general diet during pregnancy (as in other studies). Since the diet of interest was that during childhood, the data had to be collected from mothers as the children were too young to recall their diet during childhood. Childhood diet assessed was that from weaning to the age of diagnosis of type 1 diabetes, since type 1 diabetes is known to have a long preclinical course. In the case of the matched controls, diet was assessed from weaning to the same age as the respective case. Dietary intake was estimated according to the frequency of the food consumed during pregnancy (Supplementary Material 1, www.jofem.org). The questionnaire for all the mothers of type 1 diabetes patients and of controls was administered by the same interviewer to ensure uniformity of data collection. Foods included in the FFQ were milk, sweet drinks and tea, fresh fruit, dried fruit, vegetables, potatoes, uncooked cereal, rice or pasta, bread, chicken, fried chicken, fish, beef and pork, pizza, savoury cakes and pies, biscuits, packaged snacks, cakes, candy, chocolate and ice-cream. Mothers were additionally asked about their alcohol consumption during the index pregnancy. All interviews were conducted face-to-face.

The study protocol was approved by the Ethics Committee at the University of Malta, the Data Protection Officer at Mater Dei Hospital and the Data Protection Commissioner. The study was conducted in compliance with the Helsinki Declaration.

Statistical methods

We compared the food frequency of type 1 children before the diagnosis to that of controls up to the same age. We also compared maternal diet during pregnancy between cases and controls. Statistical analysis was performed using SPSS. The statistical significance of differences between cases and controls was assessed using two-tailed unpaired Student's *t*- test for normally distributed continuous variables and by the Mann-Whitney test for non-normally distributed continuous variables. We also compared the frequency of intake of food items between cases and controls using the Chi-squared test. Logistic regression was used to investigate the independent predictors of type 1 diabetes. Statistical significance was set at $\alpha = 0.05$. For the purposes of selection of co-variables for multivariate analyses, parameters which were significant or quasi-significant in monovariate analysis ($P < 0.1$) were chosen and entered in the regression analyses. Sample size was determined so as to have 0.8 statistical power to detect an effect size (Cohen's d) of 0.4 at $\alpha = 0.05$. Cohen's d is the standardized mean difference of an effect, namely the difference between observations divided by the standard deviation of these observations; setting a Cohen's d at a value of 0.4 detects a moderate effect size [24].

Results

Eighty-nine mothers of type 1 diabetes patients and 89 mothers of controls completed the modified food frequency questionnaire with regards to maternal diet, whilst 88 mothers of type 1 diabetes patients and 88 mothers of controls completed the modified food frequency questionnaire with regards to the childhood diet. One of the mothers who completed the questionnaire of diet in pregnancy of the child but was not able to provide any information on the diet of the child since the child was not living with her. Mean (± standard deviation) maternal age at delivery was 29.1 ± 5.3 years in controls and 29.3 ± 4.6 years in mothers of type 1 diabetes patients (P = 0.63). Mothers were generally healthy, but four mothers of controls and three mothers of patients with type 1 diabetes had gestational diabetes during the index pregnancy. Seven mothers in each group had pregnancy-associated hypertension. The median (interquartile range (IQR)) maternal body mass index was 28.9 (25.8 - 33.5) kg/m^2 in cases and 27.9 (24.9 - 31.9) kg/m^2 in controls (P = 0.25). The median (IQR) birth weight of cases was 2.76 (2.67 - 2.80) kg compared to 2.77 (2.68 - 2.81) kg in controls (P = 0.48). The median age at diagnosis of type 1 diabetes was 11 years (IQR 7.8 - 14.5). The study group included mothers of 48 males and 41 females.

Results for maternal diet during pregnancy

Table 1 shows the results with respect to maternal diet. Mothers of type 1 diabetes patients consumed more savoury cakes and savoury pies during pregnancy than mothers of controls, with mothers of type 1 diabetes patients having a median intake of savoury cakes and pies of 2 to 3 times a month (IQR of 0.25 - 1.0 weekly) compared to a median of once a month (IQR of 0.06 - 1.0 weekly) for the mothers of controls, the difference being statistically significant at a P value of 0.022. Mothers of type 1 diabetes patients had ice-cream during pregnancy more frequently than mothers of controls with the difference being statistically significant (P = 0.042).

There were no statistically significant differences in the average consumption of the different types of beverages (including water, milk, soft drinks, fruit juices, coffee, tea, sweetened tea and alcohol) by the mothers of type 1 diabetes patients and controls during pregnancy. Consumption of fresh fruit, dried fruit, vegetables, rice and pasta, potatoes, uncooked cereal, bread, chicken, fish, beef, pork, pizza, biscuits, packaged snacks, cakes, candy and chocolate also did not differ significantly between mothers of type 1 diabetes patients and mothers of controls.

Table 1. Summary of Results for Diet During Pregnancy in Mothers of Type 1 Diabetes Subjects and Mothers of Controls

Intake	Mothers of controls	Mothers of type 1 diabetes subjects	P value
Milk	3.5 (0 - 17.5)	7.0 (0 - 17.5)	0.222
Sweet beverages[a]	8.1 (1.5 - 3.1)	7.0 (1.5 - 27.1)	0.151
Alcohol	0 (0 - 0)	0 (0 - 0)	0.446
Coffee	7.0 (0 - 17.5)	1.0 (0 - 17.5)	0.404
Tea	7.0 (0 - 17.5)	17.5 (0 - 17.5)	0.404
Fresh fruit	14 (14 - 21)	14 (14 - 21)	0.823
Dried fruit	0 (0 - 1.0)	0 (0 - 0.625)	0.859
Vegetables	7 (3.5 - 14.0)	7.0 (3.5 - 14.0)	0.063
Potatoes	3.5 (3.5 - 3.5)	3.5 (3.5 - 3.5)	0.544
Fried potatoes	1.5 (0.5 - 2.63)	1.0 (0 - 1.75)	0.322
Uncooked cereal	3.5 (0 - 5.5)	3.5 (0.44 - 7.0)	0.193
Rice and pasta	2.0 (2.0 - 3.5)	2.0 (2.0 - 3.5)	0.859
Bread	7.0 (7.0 - 14)	7.0 (7.0 - 14.0)	0.115
Chicken	2.0 (2.0 - 3.5)	2.0 (2.0 - 2.0)	0.714
Fish	1.0 (0.25 - 1.0)	1.0 (0.25 - 1.0)	0.535
Beef and pork	2.0 (1.0 - 3.0)	2.0 (1.0 - 3.0)	0.554
Savoury cakes and pies	0.25 (0.06 - 1.0)	0.625 (0.25 - 1.0)	0.022[b]
Pizza	0.625 (0.25 - 1.0)	0.625 (0.25 - 1.0)	0.570
Biscuits	7.0 (2.0 - 7.0)	3.5 (1.0 - 7.0)	0.263
Packaged snacks	0.44 (0 - 2.0)	0.25 (0.09 - 2.0)	0.902
Cakes	2.0 (0.625 - 3.5)	1.0 (0.625 - 3.5)	0.500
Candy	0 (0 - 1.0)	0 (0 - 0.44)	0.821
Chocolate	3.5 (1.0 - 7.0)	2.75 (1.0 - 7.0)	0.673
Ice-cream	0.625 (0.25 - 1.0)	1.0 (0.44 - 3.5)	0.042[b]

Results are in median weekly intake and interquartile range. [a]Soft drinks, fruit juices, sweetened tea/coffee. [b]Significant results.

There was a greater proportion of mothers of type 1 diabetes patients who had chicken twice weekly when compared to mothers of controls with a higher proportion of the latter consuming chicken three times a week or more when compared to mothers of type 1 diabetes patients (χ^2 = 7.786, df = 2, P = 0.02). There were no differences in the frequency of intake of the other food items studied.

Results of multiple logistic regression analysis of maternal diet components with type 1 diabetes being the dependent variable and parameters which were significant or quasi-significant in univariate analysis entered as co-variates are shown in Table 2.

Table 2. Results of Multiple Logistic Regression Analysis of Maternal Diet Components as Predictors of Type 1 Diabetes

	β	SE	P value	Odds ratio
Vegetables	0.026	0.022	0.227	1.026
Ice-cream	0.176	0.097	0.070	1.192
Savoury cakes and pies	0.473	0.302	0.117	1.605

SE: standard error of the mean.

Results for childhood diet

Table 3 compares the childhood food frequency between type 1 diabetes patients and controls. Type 1 diabetic subjects were found to consume bread more frequently during childhood before disease onset than controls (median (interquartile range (IQR)) of 7 (7.0 - 14.0) weekly and 7 (7.0 - 7.0) weekly in controls (P = 0.01). A greater proportion of type 1 diabetes patients had bread twice daily or more when compared to controls (χ^2 = 18.708, df = 2, P = 0.0001).

On the other hand, type 1 diabetes patients consumed chicken less frequently than controls, at a median (IQR) of twice a week (2.0 - 3.5) compared to 3.5 (2.0 - 3.5) times a week in controls (P = 0.002). Type 1 diabetes patients ate fish at a median of once weekly (0.25 - 2.0), which was more frequent than controls, who consumed fish at a median (IQR) of 0.813 times weekly (0.0 - 1.0) (P = 0.036). When the intake of fish was stratified according to the frequency of intake, a greater proportion of type 1 diabetes patients were found to consume fish once weekly and twice weekly or more when compared to controls (χ^2 = 13.424, df = 4, P = 0.0094). Intake of beef and pork was not significantly different between type

Table 3. Summary of Results for Diet of the Child up to the Date of Diagnosis of Type 1 Diabetes

Intake	Controls	Type 1 diabetes subjects	P value
Milk	7 (6.375 - 17.5)	17.5 (7.0 - 17.5)	0.13
Sweet beverages[a]	3.25 (1.53 - 13.5)	5.25 (1.47 - 17.0)	0.45
Tea	0 (0 - 1.5)	0 (0 - 0.63)	0.98
Fresh fruit	7 (3.5 - 14)	14 (7 - 14)	0.12
Dried fruit	0 (0 - 0)	0 (0 - 0)	0.15
Vegetables	3.5 (1.35 - 7)	3.5 (0.9 - 14)	0.545
Potatoes	3.5 (3.5 - 3.5)	3.5 (3.5 - 3.5)	0.40
Fried potatoes	1.75 (0.88 - 2.0)	1.8 (0.9 - 1.8)	0.29
Uncooked cereal	7.0 (3.5 - 7.0)	7.0 (3.5 - 7.0)	0.65
Rice and pasta	2.75 (2.0 - 3.5)	2.0 (2.0 - 3.5)	1.00
Bread	7.0 (7.0 - 7.0)	7.0 (7.0 - 14.0)	0.01[b]
Chicken	3.5 (2.0 - 3.5)	2.0 (2.0 - 3.5)	0.002[b]
Fried chicken	1.0 (0 - 1.8)	1.0 (0 - 1.13)	0.12
Fish	0.813 (0 - 1.0)	1.0 (0.25 - 2.0)	0.036[b]
Beef and pork	2.0 (1.0 - 2.0)	1.5 (1.0 - 2.0)	0.78
Pizza	1.0 (0.625 - 1.0)	1.0 (0.625 - 1.0)	0.62
Biscuits	7.0 (2.0 - 7.0)	7.0 (2.0 - 7.0)	0.88
Packaged snacks	2.0 (1.0 - 7.0)	2.0 (1.0 - 5.5)	0.68
Cakes	1.0 (1.0 - 3.5)	1.5 (1.0 - 3.5)	0.76
Candy	0.82 (0 - 3.5)	0.25 (0 - 2.0)	0.21
Chocolate	3.5 (2.0 - 7.0)	3.5 (1.0 - 7.0)	0.97
Ice-cream	1.0 (0.63 - 2.0)	1.5 (1.0 - 3.5)	0.12

Results are in median weekly intake and interquartile range. [a]Soft drinks, fruit juices, sweet tea/ice-tea. [b]Significant results.

1 diabetes patients and controls (type 1 diabetes patients 2.0 (1.0 - 2.0); controls 1.5 (1.0 - 2.0) (P = 0.78)).

There were no statistically significant differences in the frequency of intake of the different beverages included in the food frequency questionnaire, namely milk, sweet drinks and tea between type 1 diabetes patients (up to the age of diagnosis) and controls (up to the same age as cases). There were also no differences in the intake of dried fruit, vegetables, potatoes, uncooked cereal, rice or pasta, pizza, savoury cakes and pies, biscuits, packaged snacks, cakes, candy or chocolate.

When foods were stratified according to frequency of intake, a greater proportion of type 1 diabetes patients had savoury cakes and pies twice weekly or more when compared to controls (χ^2 = 10.637, df = 4, P = 0.0310). There were no differences in the frequency of intake of the other food items studied.

Multiple logistic regression analysis with type 1 diabetes being the dependent variable and parameters which were significant or quasi-significant (P < 0.1) in univariate analysis being entered as co-variates showed that childhood consumption of bread was independently associated with increased risk of type 1 diabetes whilst consumption of chicken was independently associated with decreased risk (Table 4).

Discussion

In this study, the consumption of foods in type 1 diabetes patients and controls up to the age of diagnosis of type 1 diabetes was investigated. We also investigated the possible role of maternal diet during pregnancy. As discussed above, both childhood and maternal diet might be implicated in the pathogenesis of type 1 diabetes. Most previous studies have either studied maternal or childhood diet on their own. We feel that it is important to study both at the same time, since one would expect maternal and childhood diet to be closely linked. Hence any reported association in maternal diet might be mediated by the childhood dietary factors and vice-versa. Since we

Table 4. Results of Multiple Logistic Regression Analysis of Childhood Diet Components as Predictors of Type 1 Diabetes

	β	SE	P value	Odds ratio
Bread	0.098	0.041	0.018	1.103
Chicken	-0.492	0.160	0.002	0.611
Fish	0.244	0.200	0.222	1.277

SE: standard error of the mean.

found significant associations between different items in maternal diet to those in childhood diet, our data show that this possibility is unlikely. We chose to study whole foods rather than total consumption of macronutrients since foods are more complex than their macronutrient composition. The effects of food might depend on its content of additives or of unidentified chemicals such as contaminants and pollutants and on the interaction between its different constituents. Furthermore, the effects of the same type of macronutrient may vary considerably. For example, there is evidence that the biological effects of dietary protein may vary according to its amino acid constitution [25]. Glutamine, arginine, tryptophan, and citrulline have been reported to be important in the maintenance of intestinal barrier [26, 27], which is thought to be important in protecting against type 1 diabetes [28]. Arginine is also a source of polyamines [26], which have been shown to improve insulin resistance, enhance the intestinal barrier and to have modulatory effects on the gut microbiome in diet-induced obese mice [29]. On the other hand, sulphur-containing amino acids are associated with increased adiposity [30], whilst branched-chain and aromatic amino acids predict insulin resistance in young adults [31]. Both obesity and insulin resistance have been linked to type 1 diabetes [12]. Likewise, there may be differences in the biological effects of various monounsaturated fatty acids [32].

Diet in the child until the date of diagnosis and type 1 diabetes

A positive association was found between consumption of bread and fish during childhood and type 1 diabetes on univariate analysis. A novel negative association between consumption of chicken and type 1 diabetes on univariate analysis was also found. On multivariate analysis, the positive association between consumption of bread and type 1 diabetes and the negative association between consumption of chicken and type 1 diabetes remained significant. Our data therefore support the hypotheses by Landin-Olsson et al [9] that food consumption may be involved in the pathogenesis of type 1 diabetes.

The negative association between frequency of chicken consumption and type 1 diabetes in the current study may be due to a protective effect associated with the consumption of chicken itself, or indirectly via increased consumption of other dietary products in those with low chicken consumption. One possibility is that the high protein content of chicken [33] may help to induce satiety [34], which may result in a reduction in total caloric intake or in consumption of other foods that potentially increase the risk for developing type 1 diabetes. It is unlikely to be due to increased consumption of red meats since the frequency of beef and pork consumption until diagnosis was not found to be significantly associated with type 1 diabetes. Another possibility is that, in view of its low-fat content [33], chicken consumption may help reduce blood cholesterol levels. However, we do not have data on lipid levels to test this hypothesis. Nonetheless, mean population cholesterol has been found to be positively associated with the incidence of type 1 diabetes [35]. High cholesterol levels may contribute towards the development of type 1 diabetes through a predisposition to Th1 response [36], a reduction in pancreatic β-cell function [37] and increased β-cell apoptosis [38]. A high fat diet may also lead to changes in the microbiome [39].

The fact that we found an association of type 1 diabetes with bread consumption, but not with the consumption of other wheat-containing foods such as pasta suggests that the association may be mediated by bread constituents other than wheat, such as yeast and food additives. These results also highlight the importance of studying whole foods rather than macronutrients since foods are far more complex than their macronutrient composition. Very little data exist on the possible association of such non-macronutrient constituents with type 1 diabetes. However, surfactant food additives can increase intestinal permeability [40]. Increased intestinal permeability is known to precede the onset of type 1 diabetes and is thought to be causally related to it [41]. Emulsifiers can alter the gut microbiome [28], whilst sodium stearoyl lactylate, which is a commonly used emulsifier in bread, can inhibit butyrate-producing bacteria [42]. The latter are thought to protect against type 1 diabetes [43]. Our data therefore suggest that the possible role of these and other bread constituents in type 1 diabetes risk should be studied. However, in our cohort, bread was consumed more frequently than pasta. It is therefore also possible that the low consumption of pasta in our cohort explains our negative result. Gluten proteins found in wheat are partly resistant to degradation in the intestine [44], rendering them more immunogenic than other dietary proteins. Although gluten has been reported to be associated with type 1 diabetes in non-obese diabetic (NOD) mice [45] and with increased islet cell autoimmunity [46] and diminished insulin secretion in humans [47], the Diabetes Autoimmunity Study in the Young did not find any association of gluten intake after 1 year of life and islet cell autoimmunity [48]. This is consistent with the results of our study. Since the type of bread consumed by type 1 diabetes individuals and controls was not specified, it was not possible to study whether type 1 diabetes is associated with any specific type of bread. This would be of interest since different types of bread differ in their composition especially in the type of additives used.

The positive association between frequency of fish consumption and type 1 diabetes found on univariate analysis in this study is in contrast to previous reports of a protective effect of fish and fish oils with regards to type 1 diabetes. The positive association noted in our study disappeared on multivariate analysis, suggesting that it may be due to decreased consumption of other dietary components such as chicken. The type of fish consumed in the Maltese Islands, which is mainly farmed seabream, may also have contributed to the lack of protective effect of fish consumption in our study. Farmed fish has a higher n-6-to-n-3 polyunsaturated fatty acid (PUFA) ratio compared to wild fish [49]. *In vitro* studies have shown that transgenic islets with higher n-3 PUFA levels and lower n-6 PUFA levels had significantly greater glucose, amino acid and glucagon-like peptide-1 stimulated insulin secretion than the wild type and were less susceptible to cytokine-induced beta cell death [50]. Furthermore, n-6 PUFA derived eicosanoid products have strong pro-inflammatory properties [51]. A high dietary n-6-to-n-3 PUFA ratio has also been associated with higher cholesterol levels in rats. In humans, n-3 PUFA have been shown to protect against islet autoimmunity [52, 53] but not against conversion to type 1 diabetes [54]. Farmed fish also differs from wild fish in its content of elements [55, 56] and of volatiles [57]. The potential role of these constituents on type 1 diabetes risk merits further study.

We did not find any association between cow's milk protein intake and type 1 diabetes. Virtanen et al [58] reported a marginal positive association, whilst the DAISY study found an association of cow's milk consumption with increased risk of islet autoimmunity only in children with low/moderate risk HLA-DR genotypes [59]. Dietary factors associated with an increased risk for type 1 diabetes development in other studies not replicated in the present study include intake of sugar-sweetened beverages [60]. Possible reasons for these discrepancies include differences in degree of consumption of implicated food items, modulatory effects of other environmental factors and a difference in genetic risk between studied populations.

Maternal diet during pregnancy and type 1 diabetes

Our results show that mothers of type 1 diabetes patients had a higher intake during pregnancy of savoury snacks and pies including the traditional Maltese "pastizzi" as well as of ice-cream compared to control mothers on univariate analysis, both subsequently losing significance on multivariate analysis.

The common factor linking maternal consumption of pastizzi and ice-cream during pregnancy to increased risk of type 1 diabetes could be their fat content. The production of traditional Maltese "pastizzi" and other savoury snacks and pies involves the use of significant amounts of lard and butter. Butter, lard and ice-cream are all rich in cholesterol and saturated fatty acids [33]. In an ecological study, Vella et al [35] found that the mean population total cholesterol in men and women was significantly correlated with the incidence of type 1 diabetes in both boys and girls, with the association remaining significant on multivariate analysis. A high fat maternal diet during pregnancy has been shown to programme the fetus to develop hypercholesterolemia in animal studies [61]. Animal models have also shown that a high-fat diet during gestation impairs pancreatic beta-cell development [62] and insulin release [63] in the offspring possibly via impaired islet revascularization [64]. Additionally, high fat diets during gestation have also been associated with increased body mass and insulin resistance [65], both of which have been implicated in the pathogenesis of type 1 diabetes [66].

The results of this study do not show any association between maternal consumption of milk to risk of type 1 diabetes in the offspring. This may relate to the fact that skimmed or semi-skimmed milk, rather than full-cream milk, are the predominant types of milk consumed in Malta. The lack of association of other high-fat foods in the maternal diet to future type 1 diabetes risk in the offspring in these data could be due to a number of factors. These include the low consumption of some of these foods in our cohort (cakes, fried potatoes, red meat and pizza), the nature of their fat content, differences in the manufacturing processes of these various food items, as well as the presence of other constituents that might counterbalance the detrimental effects of fat. For example, flavonoids, which are found in cocoa, have been reported to protect against apoptosis of pancreatic β-cell line [67] and to prevent type 1 diabetes in NOD mice [68]. Similarly, the lower freezing temperatures required in the manufacturing of ice-cream might also alter the immunogenic properties of its constituents possibly explaining the association of type 1 diabetes with an increased consumption of ice-cream by the mother during pregnancy observed in this study. This again highlights the importance of studying whole foods, as in the present study, rather than total macronutrient intake.

Strengths and limitations

One of the major strengths of this study is that all the data of mothers of type 1 diabetes subjects and mothers of controls were collected by the same interviewer thus maximizing homogeneity of data collection. Another strength is that individuals who were identified as controls were matched for sex and date of birth eliminating potentially confounding factors with respect to seasonality of birth or due to cohort effect.

Our sample size had *a priori* statistical power of 0.8 to detect an effect size (Cohen's d) of 0.4 at $\alpha = 0.05$. Nonetheless, replication of our results in larger studies would be desirable. One major limitation of this study is recall bias as an FFQ was used to collect data in a retrospective manner and over a prolonged period until diagnosis of type 1 diabetes in the child. Furthermore, the FFQ is not always considered as being accurate. However, we chose to use it since it can be used to estimate intake over a relatively long period of time (6 months to 1 year) [23]. It is more appropriate than 24-h recall and food registration questionnaires in studying long-term impact of diet; it has also been used extensively by other authors. In the present study, it was used to include dietary assessment over several years until date of diagnosis and was modified to include consumption of foods that are characteristic of the Maltese diet. No other method has been reported to be superior to FFQs for such long-term recall. Furthermore, dietary habits have been shown to demonstrate considerable tracking over time [69]. Prospective intervention trials to investigate the role of diet are extremely difficult to conduct, especially in uncommon diseases such as type 1 diabetes.

We also have no data on the genetic factors known to affect type 1 diabetes risk. Studying genetically at-risk individuals prospectively would be helpful in increasing the number of individuals who develop type 1 diabetes, but has the disadvantage that environmental factors would be expected to play a smaller role in such a population. Furthermore, it has been shown that the role of genetic factors has decreased over time [6]. Similar to other studies [58, 59], we investigated childhood diet from weaning to the diagnosis of type 1 (or the same age in controls). The rationale for this is that type 1 diabetes is known to have a long preclinical course [7, 8]. However, we cannot exclude the possibility that exposure to some food types during critical periods in childhood might affect the risk of type 1 diabetes.

Conclusions

We found a positive association between consumption of bread and fish during childhood and a novel negative association between consumption of chicken and type 1 diabetes on univariate analysis. On multivariate analysis of the positive association between consumption of bread and type 1 diabetes and the negative association between consumption of chicken and type 1 diabetes remained significant. Maternal consumption of savoury snacks and pies and of ice-creams during pregnancy was also associated with type 1 diabetes in univariate, but not multivariate, analysis. These data support the hypothesis that dietary factors may be important in the pathogenesis of type 1 diabetes. These findings need to be confirmed by other authors and in other populations. Future studies may also consider nutrient adequacy, since certain nutrients such as alpha-linolenic acid, docosahexaenoic acid and vitamin D may be inadequate in modern diets [70]. All these have been linked to type 1 diabetes risk [53, 71].

Supplementary Material

Suppl 1. Questionnaire of frequency of the food consumed during pregnancy.

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Financial Disclosure

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Both authors were involved in study conception and design, critical analysis and appraisal and writing of the manuscript. Alexia Abela was additionally involved in data collection and inputting. All authors read and approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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