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¿Puede el consumo de alimentos fermentados tradicionales proteger contra la tiroiditis de Hashimoto?

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ABSTRACT

Background: this study examined fermented food consumption habits and the relationship between other factors and Hashimoto's thyroiditis.

Methods: the study included 90 children and their mothers, 45 of whom had HT and 45 of whom did not. Participants answered a

survey questioning about their fermented food consumption habits and the status of various environmental factors.

Results: mothers who consumed homemade pickles during pregnancy (OR: 0.341, [95 % CI: 0.117 to 0.990]) homemade yogurt (OR: 0.091, [95 % CI: 0.011 to 0.752]), tarhana (OR: 0.325 [95 % CI: 0.136 to 0.778)]) and olive oil (OR: 0.163 [95 % CI: 0.033 to 0.792]) were found to have a statistically significant lower risk of developing Hashimoto's disease in their children. The risk of HT in children who consumed homemade yogurt (OR: 0.091 [95 % CI: 0.011 to 0.752]), cheese (OR: 0.242 [95 % CI: 0.100 to 0.590]), and olive oil (OR: 0.042 [95 % CI: 0.002 to 0.750]) was found to be significantly lower than in children who did not consume it.

Conclusions: fermented food consumption habits can be protective against autoimmune diseases such as HT by affecting the immune system through the intestinal microbiota.

Keywords: Fermented foods. Hashimoto thyroiditis. Probiotics. Yogurt. Tobacco smoking.

RESUMEN

Antecedentes: este estudio examina los hábitos de consumo de alimentos fermentados y la relación entre otros factores y la tiroiditis de Hashimoto.

Métodos: el estudio incluyó a 90 niños y sus madres, 45 de los cuales tenían HTA y 45 no. Los participantes respondieron una encuesta que preguntaba por sus hábitos de consumo de alimentos fermentados y el estado de varios factores ambientales.

Resultados: se encontró que las madres que consumieron encurtidos caseros durante el embarazo (OR: 0,341, [IC del 95 %: 0,117 a 0,990]), yogur casero (OR: 0,091, [IC del 95 %: 0,011 a 0,752]), tarhana (OR: 0,325 [IC del 95 %: 0,136 a 0,778)]) y aceite de oliva (OR: 0,163 [IC del 95 %: 0,033 a 0,792]) tenían un riesgo

estadísticamente significativamente menor de desarrollar enfermedad de Hashimoto en sus hijos. El riesgo de HTA en niños que consumieron yogurt casero (OR: 0,091 [IC 95 %: 0,011 a 0,752]), queso (OR: 0,242 [IC 95 %: 0,100 a 0,590]) y aceite de oliva (OR: 0,042 [IC 95 %: 0,002 a 0,750]) fue significativamente menor que en niños que no lo consumieron.

Conclusiones: los hábitos de consumo de alimentos fermentados pueden ser protectores frente a enfermedades autoinmunes como la HTA al afectar al sistema inmunológico a través de la microbiota intestinal.

Palabras clave: Alimentos fermentados. Tiroiditis de Hashimoto. Probióticos. Yogur. Tabaquismo.

INTRODUCTION

Hashimoto's thyroiditis (HT) is an autoimmune disease that causes organ-specific destruction consisting of autoantibodies against thyroid peroxidase, thyroglobulin, and intrathyroidal mononuclear cell infiltration (1). Some researchers have demonstrated that environmental factors are essential in developing HT in individuals with genetic predisposition (2,3). Viral infecting microorganisms are also factors that trigger the disease (4). However, understanding the effects of commensal microorganisms is of the utmost importance. They are pivotal for the truthful development and function of the congenital and adaptive immune systems, and hoarded evidence indicates that the gut microbiota influences the pathogenesis of autoimmune diseases (5-7).

Fermented foods are the essential elements of human nutrition that have been reproduced since the evolution of human civilizations (8). Fermented foods often utilize controlled microbial growth and enzymatic conversion of major and minor food ingredients. Fermentation may also lead to new compounds with the potential to

modulate health. In addition, lactic acid bacteria (LAB) can release several health-modulating combinations and signaling molecules in the matrix during fermentation (9). Lactic acid is a metabolite synthesized by LAB fermentations in quantities that usually reach over 1 % (10). Lactic acid (or lactate) has lately been shown to dose-dependently reduce proinflammatory cytokine secretion in TLR-activated dendritic cells and macrophages (11). Lactate also changes the redox state by decreasing the charge of reactive oxygen types in intestinal enterocytes (8).

The International Scientific Association for Probiotics and Prebiotics recommends that the term "probiotic" be used only for products that provide live microorganisms with appropriate numbers of well-defined strains with the expectancy of providing an acceptable benefit to the host's health. According to this definition, although not all FFs qualify as probiotics, and not all probiotics are in FF format, most FFs contain bacteria that act as probiotics (12,13).

Many FF foods are widely used in traditional Turkish cuisine. Some of these are: yogurt, cheese, fermented olive oil, tarhana (baker's yeast, salt, yogurt, and various cooked vegetables are produced from wheat flour), kefir (a fermented milk product), pickles, turnip (fermented turnip and juice), and boza (reproduced from wheat, millet, corn or rice).

Our study compared the social habits and FF consumption characteristics of children with HT and healthy children and their mothers during pregnancy. Thus, we aimed to evaluate whether there is a relationship between FF consumption habits and other environmental factors with HT.

METHODS

This cross-sectional study was conducted in the XXX Pediatrics Hospital Pediatric Endocrinology outpatient clinic between January 2022 and December 2022. A total of 45 children with a diagnosis of HT between the ages of 10 and 18 volunteered to answer the

questionnaire, and 45 healthy children of the same age and their mothers were included in the study. Participation approval was obtained from the children and their families who participated in the study. HT was diagnosed with thyroid autoantibody positivity (against thyroid peroxidase and thyroglobulin) and/or findings consistent with the disease on thyroid ultrasound (heterogeneity in the thyroid gland, pseudo nodular appearance, coarsening, etc.). Thyroid function tests and antibodies (free T3, free T4, TSH, Anti TPO, anti-TG) of the children diagnosed with HT were studied in the same laboratory with the peripheral blood serum. Healthy children were those who applied to the pediatric endocrinology outpatient clinic for various reasons but did not have any pathology, had no chronic disease, had normal thyroid functions in the last 6 months, had no goiter problems, and had normal growth and development. The study was approved by the XXX University Ethics Committee (Protocol code: 2022/78).

Questionnaire

The same pediatric endocrinologist completed the questionnaires through face-to-face meetings with mothers and children from both groups. The questionnaire asked for information about many environmental factors and health history, such as place of residence, antibiotic use during pregnancy, smoking exposure during pregnancy and postnatal period, hospitalization history, presence of autoimmune disease in the family, sleep duration, screen exposure, etc. The questionnaire, previously used in other studies, was completed by the same pediatric endocrinologist through face-to-face meetings with mothers and children from both groups (14). The frequency of consumption of cheese, yogurt, fermented olives, kefir, pickles, turnip, boza, and tarhana was divided into groups as (1) daily, (2) weekly, and (3) monthly. To achieve statistically significant results, the survey results regarding FF consumption were coded and evaluated as consuming/not consuming instead of consumption frequency assessment at the evaluation stage.

Statistical analyses

All statistical analyses were performed with *R* version 4.1.2. statistical programming language (The *R* Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Before the analysis, the normality of the data was checked with the help of Shapiro-Wilk's normality test and Q-Q graphs, and the homogeneity of group variances was checked with the Levene test. Numerical data were presented as mean ± standard deviation or median along with minimum and maximum statistics, and categorical data were presented as frequency (*n*) and percentage (%). Student's t-test, Welch's *t*-test, Mann-Whitney *U*-test, Yates continuity correction chi-square test, Pearson chi-square test, and Fisher-Freeman-Halton tests were used to compare the study groups in terms of demographic and clinical characteristics. The effect of fermented foods mothers consume during pregnancy and children's current consumption on the risk of HT in children was examined with the help of the Generalized Linear Model (GLM) using both Crude and adjusted models. In the generalized linear model, the link function was log-link and the outcome variable distribution was binary. Three models were created and adjusted for parameters thought to have a possible confounding effect on HT, and the risk of developing HT due to food consumption was calculated based on these models. In the first model, corrections were made according to the child's gender and the time spent playing outside, in the second model, the child's gender and the time spent in front of the screen, and in the third model, the models were adjusted according to the child's gender and the time spent playing outside and in front of the screen. The odds ratio values obtained as a result of each model were presented with 95% confidence intervals, and the fact that the confidence interval included the value "1" showed that the relevant result was not statistically significant.

RESULTS

The study included 90 children and their mothers, 45 of whom had HT and 45 of whom did not.

Comparison of clinical and socio-demographic characteristics of participants according to study groups

Descriptive statistics for children and their parents are presented in table I. Mean age (145.40 ± 41.43 months vs. 133.47 ± 33.67 months, $p = 0.137$), body weight (41.11 ± 13.76 kg vs. 40.11 ± 16.41 kg, $p = 0.755$), height (145.77 ± 18.07 cm vs. 141.49 ± 17.55 cm, $p = 0.257$), total sleep time (9.13 ± 1.16 hours vs. 9.04 ± 1.23 hours, $p = 0.726$), and breastfeeding time (12.89 ± 9.45 months vs. 14.11 ± 7.96 months, $p = 0.509$) of children with HT and without HT were similar. Compared to children without Hashimoto's, screen time was significantly higher in children with Hashimoto's (med: 4 [range: 1 to 10 hours] vs. med: 2.5 [range: 0 to 10 hours], $p = 0.007$) was high, while the time spent playing outside the home was significantly lower (med: 1 [range: 0 to 7 hours] vs. med: 1.5 [range: 0 to 7 hours], $p = 0.010$).

The relationship between mothers' consumption of fermented foods during pregnancy and risk of HT in their children

The relationship between mothers' fermented food consumption during pregnancy and the risk of HT in their children is presented in table II. Considering the unadjusted results (crude model, Fig. 1A, first row, first column), mothers who consumed homemade pickles during pregnancy (39/45 vs. 31/45, OR: 0.341 [95 % CI: 0.117 to 0.990]), homemade yogurt (44/45 vs. 36/45, OR: 0.091 [95 % CI: 0.011 to 0.752]), tarhana (32/45 vs. 20/45, OR: 0.325 [95 % CI: 0.136 to 0.778]) and olive oil (43/45 versus 35/45, OR: 0.163 [95 % CI: 0.033 to 0.792]) were found to have a statistically significantly lower risk of developing Hashimoto's disease in their children. On the other hand, there was no statistically significant association between mothers' consumption of turnip, boza, stored yogurt, kefir, and cheese during

pregnancy and the likelihood of HT in their children. Considering the model adjusted for children's gender and the time they spent outside the home for play (adjusted model 1, Fig. 1, first row, second column), homemade pickles during pregnancy (adj. OR: 0.325 [95 % CI: 0.097 to 0.971]), homemade yogurt (adj. OR: 0.085 [95 % CI: 0.004 to 0.545]), tarhana (adj. OR: 0.277 (95 % CI: 0.103 to 0.699]) and olive oil (adj. OR: 0.186 [95 %]), the risk of developing HT in the children of mothers who consumed (CI: 0.026 to 0.835]) was significantly lower compared to those who did not consume it, and this risk was found to be higher in those who consumed supermarket yogurt (adj. OR: 7.653 [95 % CI: 1.202 to 151.341]). However, in adjusted model 1, no significant association was found between mothers' turnip consumption during pregnancy and their children's HT risk. Considering the model adjusted for children's gender and the time they spent in front of the screen (adjusted model 2, Fig. 1, first row, third column), the risk of developing HT in children of mothers who consumed homemade pickles (adj. OR: 0.284 [95 % CI: 0.080 to 0.889]), tarhana (adj. OR: 0.370 (95 % CI: 0.138 to 0.953]) and olive oil during pregnancy (adj. OR: 0.189 [95 % CI: 0.026 to 0.878]) were found to be significantly lower compared to those who did not consume it. However, in adjusted model 2, no significant association was found between mothers' consumption of turnips, homemade yogurt, and supermarket yogurt during pregnancy and the risk of Hashimoto's disease in their children. Considering the model adjusted for children's gender, time spent outside the home for play, as well as screen time (adjusted model 3, Fig. 1, first row, fourth column), the risk of developing HT in children of mothers who consumed homemade pickles (adj. OR: 0.289 [95 % CI: 0.080 to 0.928]), homemade yogurt (adj. OR: 0.119 [95 % CI: 0.006 to 0.875]) and tarhana during pregnancy (adj. OR: 0.341 (95 % CI: 0.123 to 0.901]) was significantly lower than in those who did not consume it. However, in adjusted model 3, no significant association was found between mothers' consumption of turnips, supermarket yogurt, and

olive oil during pregnancy and their children's risk of Hashimoto's disease. The results regarding mothers' boza, kefir, and cheese consumption could not be calculated for the adjusted models due to the small number of data.

The relationship between children's fermented food consumption habits and risk of Hashimoto's disease

The effect of children's fermented food consumption habits on the risk of developing Hashimoto's disease is given in table II. Considering the unadjusted results (crude model, Fig. 1A, second row, first column), the risk of HT in children who consumed homemade yogurt (44/45 vs. 36/45, OR: 0.091 [95 % CI: 0.011 to 0.752]), cheese (33/45) vs. 18/45, OR: 0.242 [95 % CI: 0.100 to 0.590]) and olive oil (45/45 vs. 36/45, OR: 0.042 [95 % CI: 0.002 to 0.750]) was found to be significantly lower than in children who did not consume it. However, no significant association was found between children's consumption of pickles, turnips, market yogurt, kefir, and tarhana and the risk of HT. Considering the model adjusted for children's gender and the time they spent outside the home for play (adjusted model 1, Fig. 1, second row, second column), the risk of developing Hashimoto's disease was significantly lower in children who consumed homemade yogurt (adj. OR: 0.098 [95 % CI: 0.005 to 0.589]), kefir (adj. OR: 0.290 [95 % CI: 0.072 to 0.986]) and cheese (adj. OR: 0.235 [95 % CI: 0.087 to 0.594]) compared to those who did not consume it. The model adjusted for children's gender and time spent in front of the screen (adjusted model 2, Fig. 1, second row, third column) and the model adjusted for gender, time spent outside playing, and time spent in front of the screen (adjusted model 3, Fig. 1, second row, fourth column), it was seen that the risk of developing Hashimoto's disease was significantly lower in children who consumed only cheese compared to those who did not consume cheese (adj. OR: 0.263 [95 % CI: 0.096 to 0.681] and adj. OR: 0.278 [95 % CI: 0.100 to 0.731], respectively). Results regarding children's consumption of

boza (calculations were not made in the Crude model because the number of children consuming boza was insufficient), market yogurt, and olive oil could not be calculated for corrected models due to the small number of data.

Further analysis: the effect of some fermented foods and children's gender, time spent in front of screens, and time spent outside playing on the risk of developing Hashimoto's disease

Generalized linear models were established to see the effects of some fermented foods mothers consume during pregnancy, children's gender, the time they spend in front of the screen, and the time they spend outside playing on the risk of developing Hashimoto's disease in children. The results of mothers consuming pickles, tarhana, and olive oil (other foods were not visualized due to missing observations or analysis results or were found to be statistically insignificant in previous studies, Table II) were presented visually. According to the results, girls have a higher risk of HT than boys, and it has been observed that increasing the time spent playing outside the home reduces the risk of developing HT but this risk increases with the increase in time spent in front of the screen (Fig. 2).

DISCUSSION

In our study, the risk of HT in children of mothers who consumed pickles, homemade yogurt, and olive oil during pregnancy was significantly lower. It was also found that the risk of HT was lower in children who consumed homemade yogurt, olive oil, and cheese. When we evaluated the data with adjusted models and the significantly increased risk for HT in the female gender, the increase in time spent playing outside and the decrease in time spent in front of the screen were the most critical factors in the risk of developing HT. In the adjusted models, we observed the risk-reducing effects of fermented food consumption, although generally at different rates.

Hashimoto's thyroiditis (HT) is the most widespread autoimmune thyroid disease worldwide. Microbiota changes may easily affect thyroid homeostasis. In addition to genetic and environmental influences, there is also an argument that the occurrence and progression of autoimmune thyroid disorders can be significantly affected by an altered gut microbial composition and even by overt dysbiosis (15).

Fermented milk products can modulate many immunological mechanisms with probiotic effects. Some studies have attempted to modify the progression of different inflammatory and atopic disorders in which the immune system plays a key role. Although not specific to HT, studies have been conducted on the linkage between nutrition and some diseases known to be autoimmune-based. Amital et al. (16) studied this effect in an animal model of antiphospholipid syndrome (APS) by supplementing the daily intake of animals with a probiotic blend (containing yogurt and Actimel®). The level of autoantibodies was markedly suppressed ($p < 0.05$) in mice fed Actimel® and yogurt. Actimel® and yogurt have demonstrated an immunological effect on Balb/c mice inoculated with beta2GPI to induce APS disease. Our study demonstrated the effects of fermented dairy products such as yogurt and cheese on reducing the risk of HT.

However, FF may have various potential benefits over probiotic supplements or foods. It has been demonstrated that the metabolites produced by the gut microbiota, such as SCFA, soar in plasma and stool samples after consuming yogurt (17). It has also been proposed that SCFA may have anti-inflammatory features (18). It has been suggested that factors affecting the gut microbiota and SCFA production may influence immune and inflammatory responses. (19)

In addition, tryptophan, an essential amino acid, exists in foods such as fish, red meat, yogurt, eggs, and many vegetables (12). The immunomodulatory indoleamine 2,3-dioxygenase enzyme transforms tryptophan to kynurenine, and indoleamine 2,3-dioxygenase activity is associated with suppression of T-cell responses, promotion of T

regulatory (Treg) cells, and immunity (12). Overstimulated CD4+ T-cells are known to play a major role in the pathogenesis of HT. T-cells have two functions in the pathogenesis of HT. Helper type 2 (Th2) cells lead to overstimulation and production of B-cells and plasmatic cells that produce antibodies against thyroid antigens leading to thyroiditis (20). Although we did not evaluate FF metabolites in our study, we showed that many FFs, especially yogurt, reduce the risk of HT. However, more in-depth studies on the mechanisms of FF effect are necessary.

Maternal dietary changes during pregnancy, including calorie restriction, micronutrient intake, and macronutrient intake, result in early-life conformation that can have long-term effects on the child (21). For instance, a recent study showed that maternal dietary quality during pregnancy was associated with the dietary quality of 14-year-old teenagers (22). These results indicate that maternal nutrition during pregnancy and lactation is probably essential for the health and disease of the offspring.

Recent studies have suggested that microbial transfer from mother to offspring may begin during pregnancy and arrange a precursor microbiome. In a normal, healthy pregnancy, microbial DNA can be detected in amniotic fluid, placenta and umbilical cord, fetal membranes, blood, and meconium (23). In our study, there was a significant relationship between mothers' fermented food consumption habits during pregnancy and their children's risk of HT since the mothers' pregnancy period, which may cause controversy regarding the safety of the answers given by the mothers. However, most mothers stated that their pregnancy and current habits were similar.

Breast milk is a fully adapted nutritional resource for the newborn and a practical set of immune-active molecules that deal with infections and generate mucosal immune responses. Breastfeeding has been linked to a reduced incidence of autoimmune diseases (for example, diabetes, multiple sclerosis, celiac disease, and asthma), which is

thought to be through protection against anti-inflammatory properties, early infections, antigen-specific tolerance induction, and regulation of the infant's microbiome (24). In our study, the breastfeeding duration of children in the HT group was shorter than that of healthy children, although not significantly. However, the duration of the exclusive breastfeeding period is significantly shorter in children with HT.

Numerous studies have pointed out that smoking causes different effects on the thyroid gland. Although there are debates that both active and passive smoking during pregnancy can alter maternal and fetal thyroid function, further studies are needed to clarify the effects of smoking on thyroid pathophysiology. The effect of smoking on Hashimoto's thyroiditis has not been as well documented as in Graves' disease. In addition, studies have shown that the presence of thyroglobulin antibodies, thyroid peroxidase antibodies, and hypothyroidism is lower in smokers (25). However, the fact is that one or more of the more than 4000 chemicals found in tobacco can affect fetal immune regulation. In our study, we found that active or passive smoking was significantly higher during pregnancy and postnatal period in HT group mothers.

Clarke et al. (26) noted that occupancy in rural areas that were less “clean” in early childhood substantially decreased the risk of forming papillary thyroid cancer in adulthood. In recent years, many studies have addressed the relationship between environmental infections (mostly parasitic) and autoimmune diseases (inflammatory bowel and multiple sclerosis) (27,28), suggesting that exposure to microbes affects the immune system and modulates host overreactions. In our study, when we questioned the frequency of village visits of the participants, we showed that the visits were significantly less in the HT group. In addition, children in the healthy group had longer time to play outside with friends and shorter screen time.

Existing studies have shown that house dust is an essential source of exposure to environmental microorganisms. The house dust

microbiota is an important modulator of immune metabolic and cellular functions that respond to inflammatory signals associated with human diseases (29). Studies also show that spending time outdoors can protect against multiple sclerosis, allergic diseases, and chronic diseases (30-32). Additionally, increased screen time, in addition to causing you to stay at home longer, may also be associated with an increased risk of HT due to stress triggers in the content watched and exposure to blue light. More comprehensive studies are needed on this subject.

Our study has some shortcomings that require further research. It did not analyze the effects of intake volume but only whether some of the fermented foods were consumed. Another limitation is that the population included in the study was not very large and was selected from an urban area in Turkey, so our findings may not be generalizable or adaptable to other populations.

In conclusion, as far as we know, this study is the first analysis from Turkey to evaluate the frequency of Turkish FF consumption among children with HT and healthy children. FF consumption may be associated with HT, along with other environmental factors we examined in our study, such as smoking exposure, sleep habits, screen time, frequency of illness, and village visits etc. Studies with more extensive series, including their conversion to microbiota, are needed to evaluate the efficacy of FF consumption on the pathogenesis of HT.

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Table I. The demographical and clinical characteristics of children and mothers

	Children with Hashimoto (*n* = 45)	**Children without Hashimoto (*n* = 45)**	***p*-value**
Child characteristics			
Age (months)	145.40 ± 41.43	133.47 ± 33.67	0.137[1]
Height (cm)	145.77 ± 18.07	141.49 ± 17.55	0.257[1]
Height SD	–0.04 ± 1.42	–0.20 ± 1.00	0.532[2]
Weight (kg)	41.11 ± 13.76	40.11 ± 16.41	0.755[1]
Weight SD	–0.01 ± 1.39	0.07 ± 1.00	0.757[1]
Gender (male/female)	8 (17.8)/37 (82.2)	18 (40)/27 (60)	0.036[3]
Time spent on screen (hours/day)	4 [1-10]	2.5 [0-10]	0.007[4]
Total sleep time (hours/day)	9.13 ± 1.16	9.04 ± 1.23	0.726[1]
Outdoor play time (hours/day)	1 [0-7]	1.5 [0-7]	0.010[4]
Number of siblings			0.502[3]
1 or 2	13 (28.9)	17 (37.8)	
≥ 3	32 (71.1)	28 (62.2)	
Duration of breastfeeding (months)	12.89 ± 9.45	14.11 ± 7.96	0.509[1]
Duration of only breastfeeding (months)	3.40 ± 2.63	4.82 ± 1.92	0.004[2]
Consumption of fast-food	15 (33.3)	29 (64.4)	0.006[3]
Using antibiotics in the first year	10 (22.2)	5 (11.1)	0.258[3]
Hospitalization	22 (48.9)	12 (26.7)	0.046[3]
Have tooth decay	24 (53.3)	21 (46.7)	0.673[3]
Infection in the first year of life	6 (13.3)	11 (24.4)	0.281[3]
Mother and family characteristics			
Mode of delivery			0.272[5]
Vaginal delivery	24 (53.3)	31 (68.9)	
Emergency cesarean	14 (31.1)	8 (17.8)	
Elective cesarean	7 (15.6)	6 (13.3)	
Using antibiotics during	5 (11.1)	12 (26.7)	0.106[3]

pregnancy			
Residential area			> 0.999[6]
City	43 (95.6)	43 (95.6)	
Country	1 (2.2)	0 (0)	
Village	1 (2.2)	2 (4.4)	
Features of the building they live in (apartment/house with garden)	37 (82.2)/8 (17.8)	32 (71.1)/13 (28.9)	0.319[3]
Number of children in the family			> 0.999[3]
1 or 2	29 (64.4)	30 (66.7)	
≥ 3	16 (35.6)	15 (33.3)	
Family history of Hashimoto	17 (37.8)	27 (60)	0.058[3]
Autoimmune disease in the family	20 (44.4)	29 (64.4)	0.090[3]
Pet ownership	9 (20)	13 (28.9)	0.058[3]
Smoking during pregnancy			0.020[6]
None	15 (33.3)[a]	25 (55.6)[b]	
Passive	23 (51.1)	19 (42.2)	
Active	7 (15.6)[a]	1 (2.2)[b]	
Smoking during postnatal period			0.007[6]
None	16 (35.6)	25 (55.6)	
Passive	22 (48.9)	20 (44.4)	
Active	7 (15.6)[a]	0 (0)[b]	

[1]Student's *t*-test; [2]Welch's *t*-test; [3]Chi-square test with Yates continuity correction; [4]Mann-Whitney *U*-test; [5]Pearson's chi-square test; [6]Fisher-Freeman-Halton test. Data were summarized as mean ± standard deviation or median with ranges [minimum-maximum] for numerical variables, as appropriate, and categorical variables were described as count (*n*) and percentage (%).

Table II. Association between maternal and children daily intake of foods, and the risk of Hashimoto's disease

	Children without Hashimoto (*n* = 45)	**Children with Hashimoto (*n* = 45)**	**Crude OR (95 % CI)**	**Adjusted OR[1] (95 % CI)**	**Adjusted OR[2] (95 % CI)**	**Adjusted OR[3] (95 % CI)**
For mothers during pregnancy						
Pickle (*n* = 70)	39 (86.7)	31 (68.9)	0.341 (0.117-0.990)*	0.325 (0.097-0.971)*	0.284 (0.080-0.889)*	0.289 (0.080-0.928)*
Turnip (*n* = 9)	7 (15.6)	2 (4.4)	0.252 (0.049-1.290)	0.280 (0.038-1.307)	0.394 (0.053-1.935)	0.359 (0.047-1.817)
Boza (*n* = 1)	1 (2.2)	0 (0)	0.326 (0.013-8.218)	NA	NA	NA
Homemade yogurt (*n* = 80)	44 (97.8)	36 (80)	0.091 (0.011-0.752)*	0.085 (0.004-0.545)*	0.156 (0.008-1.042)	0.119 (0.006-0.875)*
Yogurt (*n* = 8)	1 (2.2)	7 (15.6)	8.105 (0.954-68.875)	7.653 (1.202-151.341)*	5.166 (0.767-104.081)	5.410 (0.802-108.367)
Kefir (*n* = 4)	4 (8.9)	0 (0)	0.101 (0.005-1.940)	NA	NA	NA
Cheese (*n* = 86)	45 (100)	41 (91.1)	0.101 (0.005-1.940)	NA	NA	NA
Tarhana (*n* = 52)	32 (71.1)	20 (44.4)	0.325 (0.136-0.778)*	0.277 (0.103-0.699)*	0.370 (0.138-0.953)*	0.341 (0.123-0.901)*
Olive oil (*n* = 78)	43 (95.6)	35 (77.8)	0.163 (0.033-0.792)*	0.186 (0.026-0.835)*	0.189 (0.026-0.878)*	0.220 (0.029-1.075)
For infants						
Pickle (*n* = 75)	37 (82.2)	38 (84.4)	1.174 (0.387-3.564)	0.902 (0.265-3.019)	0.856 (0.250-2.905)	0.860 (0.246-2.973)
Turnip (*n* = 24)	16 (35.6)	8 (17.8)	0.392 (0.147-1.042)	0.447 (0.151-1.259)	0.427 (0.139-1.233)	0.434 (0.139-1.277)
Boza (*n* = 0)	-	-	NA	NA	NA	NA
Homemade yogurt (*n* = 80)	44 (97.8)	36 (80)	0.091 (0.011 – 0.752)*	0.098 (0.005-0.589)*	0.182 (0.009-1.149)	0.158 (0.008-1.034)
Yogurt (*n* = 8)	0 (0)	8 (17.8)	20.627 (1.152-	NA	NA	NA

			369.195)			
Kefir (n = 15)	11 (24.4)	4 (8.9)	0.302 (0.088-1.033)	0.290 (0.072-0.986)*	0.317 (0.077-1.096)	0.324 (0.078-1.146)
Cheese (n = 51)	33 (73.3)	18 (40)	0.242 (0.100-0.590)*	0.235 (0.087-0.594)*	0.263 (0.096-0.681)*	0.278 (0.100-0.731)*
Tarhana (n = 81)	42 (93.3)	39 (86.7)	0.464 (0.109-1.985)	0.407 (0.073-1.825)	0.391 (0.064-1.896)	0.390 (0.059-1.993)
Olive oil (n = 81)	45 (100)	36 (80)	0.042 (0.002-0.750)*	NA	NA	NA

[1]Adjusted for gender and time spent outside; [2]adjusted for gender and time spent on screen; [3]adjusted for gender, time spent outside, and time spent on screen. *Denotes statistical significance. NA: not applicable; OR: odds ratio; CI: confidence interval.

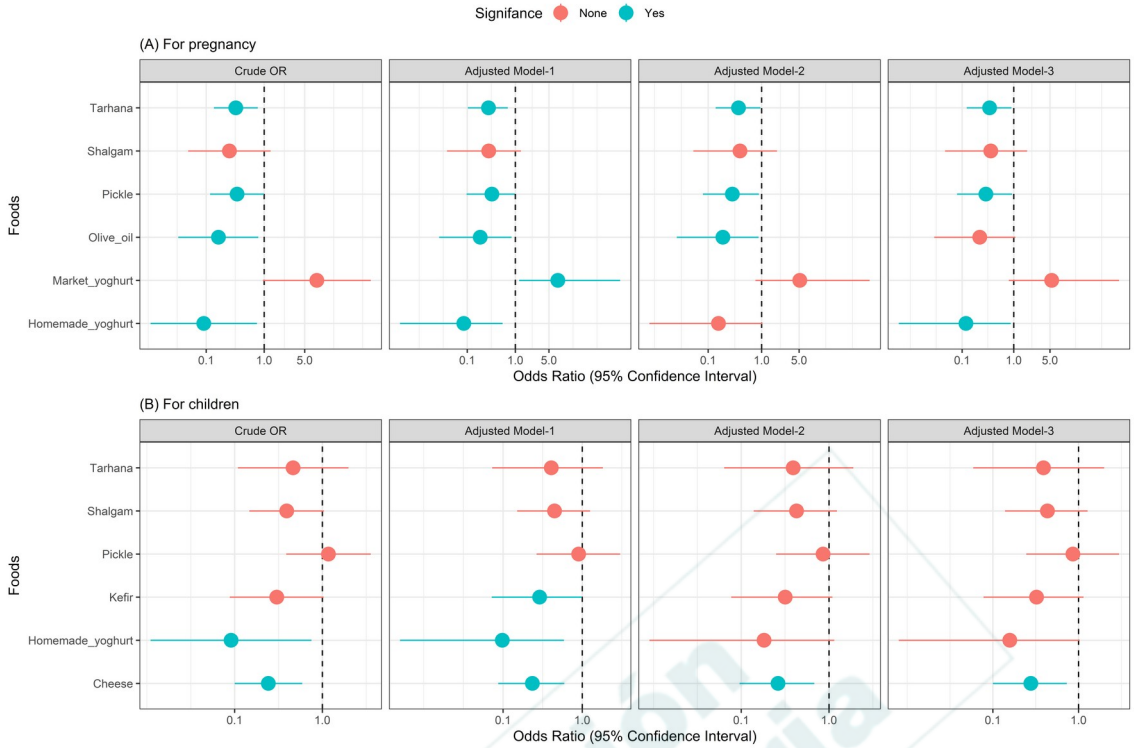

Figure 1. Adjusted odds ratios (ORs) with 95 % confidence intervals (95 % CIs) for the risk of Hashimoto disease. Adjusted Model 1 was adjusted for sex and time spent outside playing. Adjusted Model 2 were adjusted for sex and time spent on screen. Adjusted Model 3 was adjusted for sex, time spent outside playing, and time spent on screen.

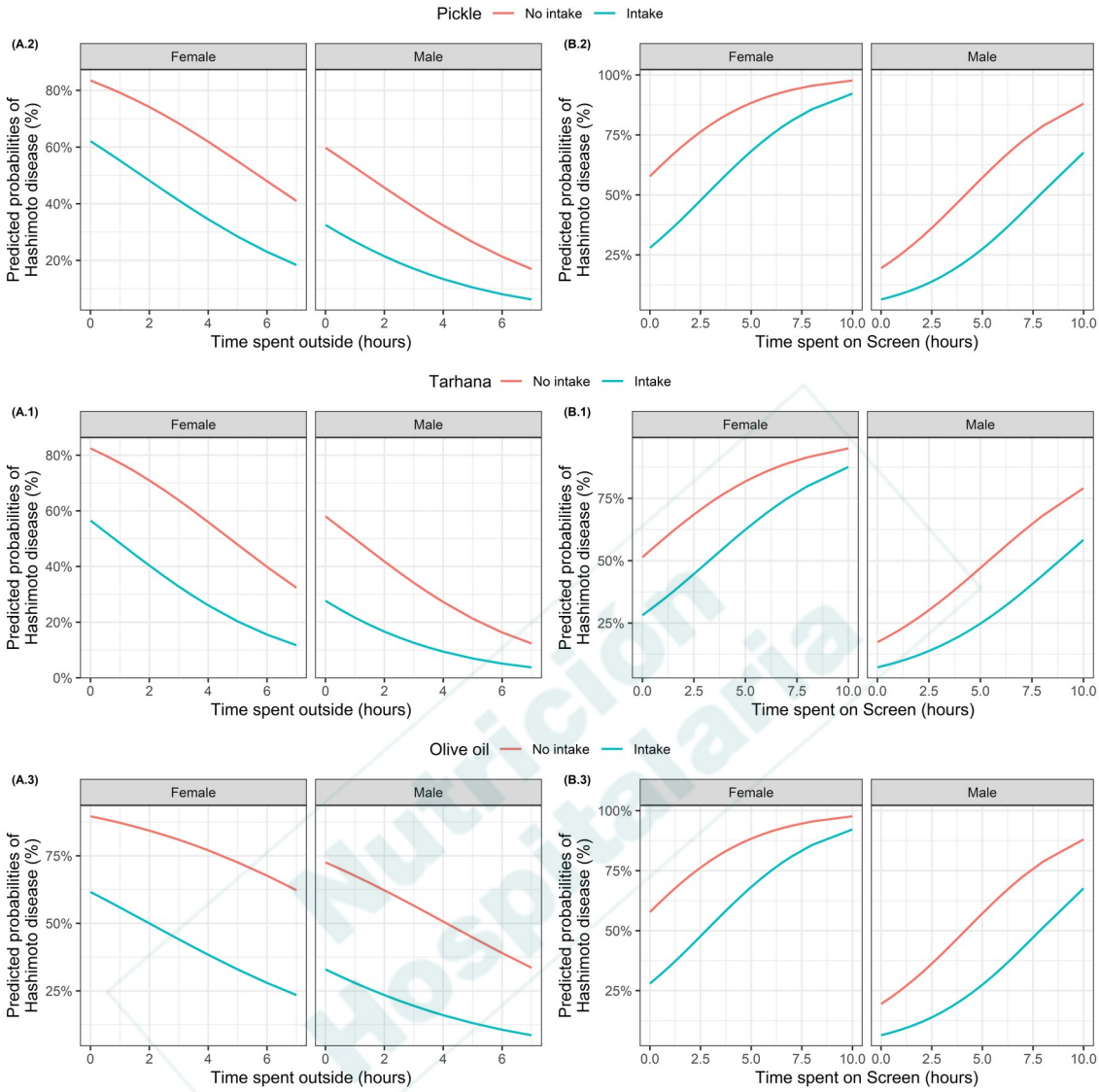

Figure 2. Marginal effect plots with the effect of changes in the time spent outside for playing and time spent on screen stratified by sex of children for foods on the predicted risk of development of Hashimoto disease in children from a multiple generalized linear model considering binomial distribution.