

Dietary vitamin C intake and the risk of islet autoimmunity and type 1 diabetes: The Environmental Determinants of Diabetes in the Young (TEDDY) Study

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Supplementary Fig. 1 Participant flow chart

Supplementary Fig. 2 The shape of association between vitamin C intake and a) Islet autoimmunity (IA), b) IAA-first, c) GADA-first, d) multiple IA based on linear and restricted cubic splines (RC-splines) showing confidence intervals and distribution of vitamin C intake among users

Supplementary Table 1 The risk of type 1 diabetes related outcomes associated with vitamin C intake followed up to 6 years of age

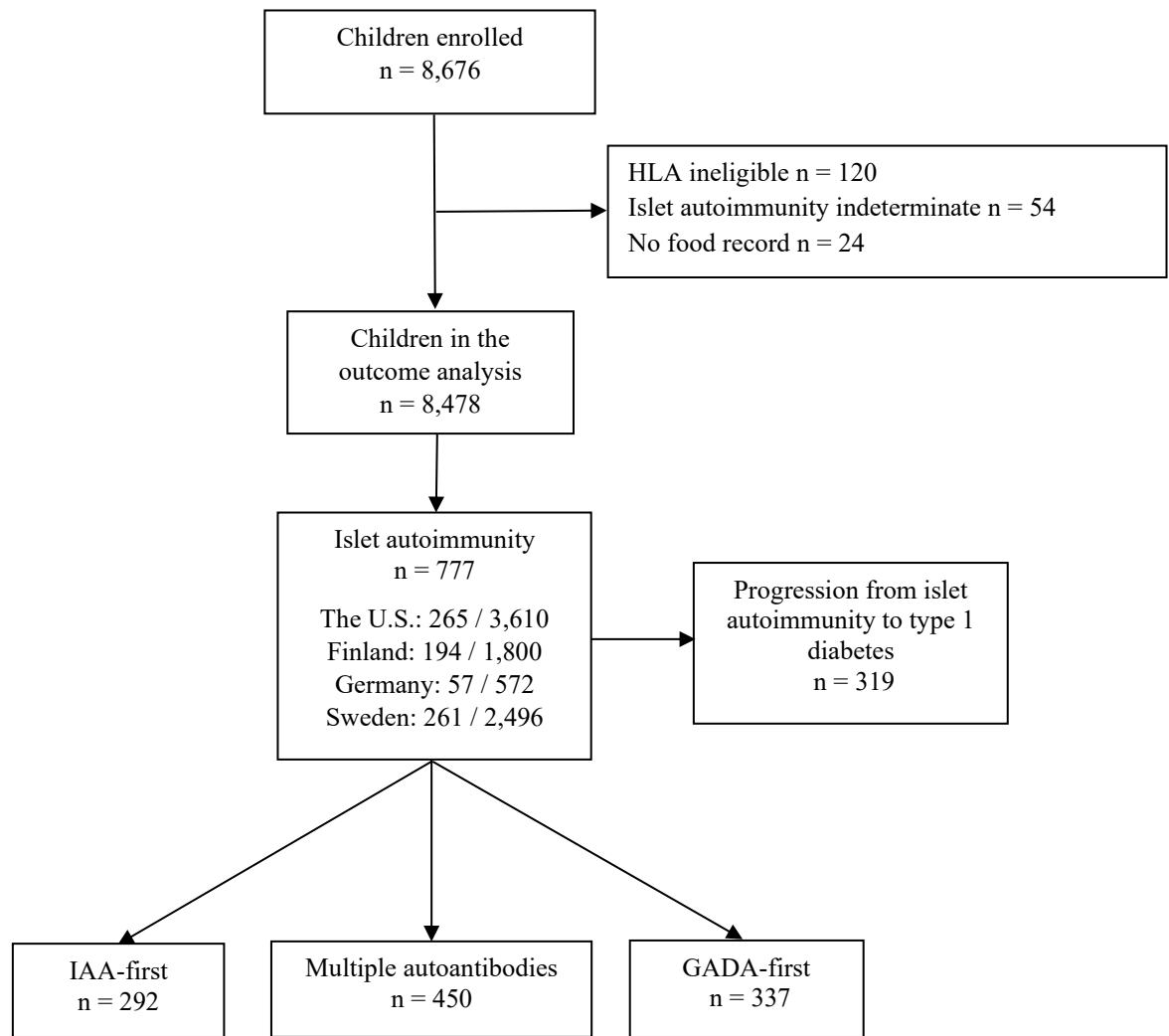
Supplementary Table 2 Interaction by time between vitamin C intake and the outcomes by months and years

Supplementary Table 3 The association between vitamin C metabolism related SNPs and the risk of islet autoimmunity (IA) outcomes and progression from IA to type 1 diabetes outcomes

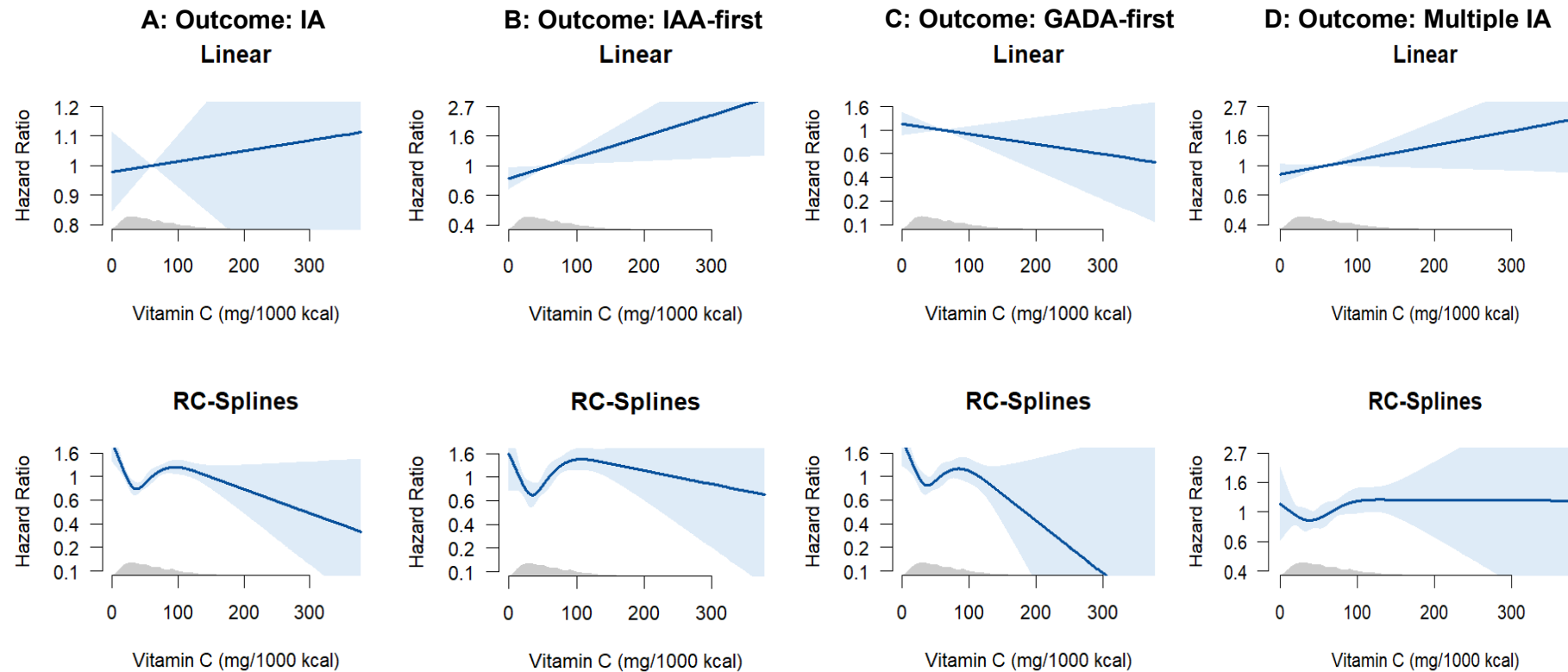
Supplementary Table 4 Interaction between background variables and vitamin C intake on plasma ascorbic acid concentrations

Supplementary Table 5 Interaction between vitamin C metabolism related genes and energy adjusted vitamin C intake on plasma ascorbic acid concentrations

Supplementary material: The TEDDY Study Group



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Supplementary Fig. 2 The shape of association between vitamin C intake and a) Islet autoimmunity (IA), b) IAA-first, c) GADA-first, d) multiple IA based on linear and restricted cubic splines (RC-splines) showing confidence intervals and distribution of vitamin C intake among users

Supplementary Table 1 The risk of type 1 diabetes related outcomes associated with vitamin C intake followed up to 6 years of age

		IA		IAA-first		GADA-first		Multiple IA		Progression to type 1 diabetes	
		HR ^a (95% CI)	P-value	HR ^a (95% CI)	P-value	HR ^a (95% CI)	P-value	HR ^a (95% CI)	P-value	HR ^b (95% CI)	P-value
Vitamin C intake											
+10 mg		1.00 (0.97-1.02)	0.782	1.03 (1.00-1.07)	0.077	0.97 (0.93-1.01)	0.122	1.02 (0.99-1.05)	0.206	0.99 (0.95-1.03)	0.749
T ₁		1.13 (0.90-1.42)	0.496	1.04 (0.74-1.48)	0.463	1.65 (1.14-2.38)	0.028	0.98 (0.72-1.32)	0.277	1.02 (0.74-1.39)	0.378
T ₂		1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T ₃		1.12 (0.89-1.40)		1.22 (0.88-1.69)		1.39 (0.95-2.05)		1.20 (0.91-1.60)		0.82 (0.60-1.13)	
+10 mg/1000 kcal ^c		1.00 (0.98-1.03)	0.653	1.03 (1.00-1.06)	0.056	0.98 (0.93-1.02)	0.324	1.03 (1.00-1.06)	0.049	1.00 (0.96-1.04)	0.973
T ₁ ^c		1.19 (0.95-1.49)	0.285	1.07 (0.76-1.52)	0.575	1.36 (0.95-1.95)	0.231	0.94 (0.70-1.26)	0.491	0.76 (0.54-1.05)	0.194
T ₂ ^c		1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T ₃ ^c		1.15 (0.91-1.44)		1.19 (0.86-1.66)		1.13 (0.78-1.64)		1.12 (0.84-1.48)		0.81 (0.60-1.10)	

^a Adjusted for HLA haplogenotype, family history of type 1 diabetes, sex, and country.

^b Adjusted for age at seroconversion, HLA haplogenotype, family history of type 1 diabetes, sex, and country.

^c Further adjusted for energy by nutrient density method

Supplementary Table 2 Interaction by time between vitamin C intake and the outcomes by months and years

	IA		IAA-first		GADA-first		Multiple IA		Progression to type 1 diabetes	
	Visit, months	Visit, years	Visit, months	Visit, years	Visit, months	Visit, years	Visit, months	Visit, years	Visit, months	Visit, years
	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Follow-up to 10 years										
Absolute intake, median	0.75	0.93	0.75	0.51	0.03	0.03	0.20	0.17	0.04	0.03
Energy-adjusted intake, median	0.91	0.37	0.99	0.34	0.17	0.27	0.32	0.15	0.07	0.10
Follow-up to 6 years										
Absolute intake, median	0.34	0.69	0.59	0.40	0.01	0.01	0.99	0.76	0.39	0.19
Energy-adjusted intake, median	0.38	0.90	0.70	0.34	0.08	0.16	0.88	0.53	0.59	0.53

Supplementary Table 3 The association between vitamin C metabolism related SNPs and the risk of islet autoimmunity (IA) outcomes and progression from IA to type 1 diabetes outcomes

			IA cases <i>n</i> =777			IAA-first cases <i>n</i> =292			GADA-first cases <i>n</i> =337			Multiple IA cases <i>n</i> =450			Progression to type 1 diabetes cases <i>n</i> =319			
Gene allele)	SNP	(minor allele)	Genotype (% of children by genotype)	HR ^a (95% CI)	P- value		HR ^a (95% CI)	P- value		HR ^a (95% CI)	P- value		HR ^a (95% CI)	P- value		HR ^b (95% CI)	P- value	
<i>SLC23A2</i>	rs1715379	(A)	GG (25.47) GA (50.11) AA (24.43)							1 (ref) 1.08 (0.81-1.45) 0.66 (0.45-0.99)	0.024							
<i>SLC2A4</i>	rs5412	(A)	GG (68.12) GA (28.27) AA (3.61)													1 (ref) 0.69 (0.51-0.93) 0.54 (0.27-1.08)	0.020	
<i>SLC2A5</i>	rs3004245	(C)	AA (31.58) AC (48.64) CC (19.78)							1 (ref) 0.68 (0.51-0.90) 0.94 (0.67-1.31)	0.017							
<i>GSTP1</i>	rs79512139	(A)	GG (83.46) GA (15.91) AA (0.63)													1 (ref) 1.43 (1.03-2.00) 3.04 (0.73-12.65)	0.043	
<i>HP</i>	rs8062041	(G)	AA (12.98) AG (46.47) GG (40.55)				1 (ref) 0.73 (0.51-1.03) 0.59 (0.41-0.85)	0.019										
<i>HP</i>	rs5467	(A)	GG (63.80) GA (32.15) AA (4.05)													1 (ref) 1.34 (0.99-1.80) 1.79 (1.02-3.14)	0.037	
<i>SOD2</i>	rs11752345	(A)	GG (58.76) GA (35.90) AA (5.35)										1 (ref) 1.31 (1.04-1.65) 1.55 (1.00-2.41)	0.025				

^a Adjusted for HLA haplogenotype, family history of type 1 diabetes, sex, country, and the first two principal components.

^b Adjusted for age at seroconversion, HLA haplogenotype, family history of type 1 diabetes, sex, country, and the first two principal components.

Supplementary Table 4 Interaction between background variables and vitamin C intake on plasma ascorbic acid concentrations

Background variables	P-value for interaction ^a	Association between vitamin C intake and plasma ascorbic acid concentrations	
		GEE Estimate (SE)	P-value
Country	<0.001		
The U.S.		0.0409 (0.0046)	<0.001
Finland		0.0351 (0.0028)	<0.001
Germany		0.0118 (0.0056)	0.034
Sweden		0.0137 (0.0031)	<0.001

^a Adjusted for energy adjusted vitamin C intake, energy intake, sex, HLA haplogenotype, family history of type 1 diabetes, and country.

Supplementary Table 5 Interaction between vitamin C metabolism related genes and energy adjusted vitamin C intake on plasma ascorbic acid concentrations

Gene SNPs	Genotype children genotype)	(% of by	P-value interaction ^a	for	Association between vitamin C intake and plasma ascorbic acid concentrations		
					GEE (SE)	Estimate	P-value
<i>SLC23A2</i> rs6037988	CC (33.24)		0.041		0.0236 (0.0036)		<0.001
	CT (49.40)				0.0307 (0.0028)		<0.001
	TT (17.36)				0.0279 (0.0043)		<0.001
<i>SLC2A1</i> rs3820546	GG (21.51)		0.034		0.0239 (0.0044)		<0.001
	GA (47.29)				0.0272 (0.0027)		<0.001
	AA (31.20)				0.0327 (0.0037)		<0.001
<i>SLC2A4</i> rs5415	TT (48.06)		0.019		0.0328 (0.0027)		<0.001
	TA (41.72)				0.0265 (0.0030)		<0.001
	AA (10.21)				0.0156 (0.0060)		0.010
<i>SOD2</i> rs56340441	AA (86.18)		0.037		0.0299 (0.0021)		<0.001
	AG (13.15)				0.0198 (0.0051)		0.001
	GG (0.67)				-0.0010 (0.0128)		0.939

^aAdjusted for dietary vitamin C intake, energy intake, sex, HLA haplogenotype, family history of type 1 diabetes, country, and the first two principal components.

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