Sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA) and type 2 diabetes

Josefin E Löfvenborg[1], Tomas Andersson[1,2], Per-Ola Carlsson[3], Mozhgan Dorkhan[4], Leif Groop[4], Mats Martinell[5], Tiinamaija Tuomi[6], Alicja Wolk[1] and **Sofia Carlsson[1]**

[1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Center for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden, [3]Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [4]Department of Clinical Sciences, Lund University, Malmö, Sweden, [5]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden, and [6]Endocrinology, Abdominal Centre, Helsinki University Hospital, Research Program for Diabetes and Obesity, University of Helsinki, and Finnish Institute for Molecular Medicine, University of Helsinki, Helsinki, Finland

Correspondence should be addressed to J E Löfvenborg
Email
josefin.lofvenborg@ki.se

Abstract

Objective: Sweetened beverage intake is associated with increased risk of type 2 diabetes, but its association with autoimmune diabetes is unclear. We aimed to investigate sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA); autoimmune diabetes with features of type 2 diabetes.
Design/methods: Data from a Swedish population-based study was used, including incident cases of LADA ($n = 357$) and type 2 diabetes ($n = 1136$) and randomly selected controls ($n = 1371$). Diabetes classification was based on onset age (≥35), glutamic acid decarboxylase autoantibodies (GADA) and C-peptide. Sweetened beverage intake information was derived from a validated food frequency questionnaire. ORs adjusted for age, sex, family history of diabetes, education, lifestyle, diet, energy intake and BMI were estimated using logistic regression.
Results: Daily intake of >2 servings of sweetened beverages (consumed by 6% of participants) was associated with increased risk of LADA (OR: 1.99, 95% CI: 1.11–3.56), and for each 200 mL daily serving, OR was 1.15 (95% CI: 1.02–1.29). Findings were similar for sugar-sweetened (OR: 1.18, 95% CI: 1.00–1.39) and artificially sweetened beverages (OR: 1.12, 95% CI: 0.95–1.32). Similarly, each daily serving increment in total sweetened beverage conferred 20% higher type 2 diabetes risk (95% CI: 1.07–1.34). In type 2 diabetes patients, high consumers displayed higher HOMA-IR levels (4.5 vs 3.5, $P = 0.0002$), but lower HOMA-B levels (55 vs 70, $P = 0.0378$) than non-consumers. Similar tendencies were seen in LADA.
Conclusions: High intake of sweetened beverages was associated with increased risk of LADA. The observed relationship resembled that with type 2 diabetes, suggesting common pathways possibly involving insulin resistance.

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Introduction

Sugar-sweetened beverage intake has been linked to increased risk of type 2 diabetes in numerous studies (1, 2, 3, 4, 5, 6); the most recent meta-analysis found that the risk increases by 13% for an increment of each serving per day in intake (7). Suggested routes by which sugar-sweetened beverages may influence diabetes risk are through glycemic or insulinemic responses or by contributing to excessive energy intake (8, 9). Artificially sweetened beverages have also been associated with an increased risk of type 2 diabetes (1, 10), although they contain no calories and are thus adding neither to the glycemic load nor to the total daily energy intake (11). Suggested mechanisms related to artificially sweetened beverages include enhanced appetite by distortion of

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satiety signaling (11) and deteriorated glucose tolerance provoked by alterations in gut microbiota (12).

The association between sweetened beverages and autoimmune diabetes is less clear (13, 14), but a recent study suggests that intake of sugar-sweetened beverage may increase the risk of type 1 diabetes in genetically susceptible individuals (13). Possible mechanistic pathways for its involvement in autoimmune processes include induced beta cell apoptosis (15), which could be due to toxic levels of glucose (16), induced oxidative stress (17) or an overloaded beta cell possibly leading to it being more visible to the immune system (18).

Latent autoimmune diabetes in adults (LADA) is a hybrid form of diabetes with features of both type 1 and type 2 diabetes. In addition to sharing autoimmune markers (typically glutamic acid decarboxylase antibodies (GADA)) with type 1 diabetes patients, LADA patients also present with (mild to moderate) insulin resistance, a feature shared with type 2 diabetes (19). Thus, it is possible that intake of sweetened beverages may influence the risk of LADA through mechanisms related to either autoimmune processes or insulin resistance, but this remains to be explored. LADA accounts for 9% of all adult-onset diabetes (20) and therefore constitutes an important part of the diabetes spectrum. Still, potential risk factors remain largely unexplored.

We aimed to investigate the risk of LADA and type 2 diabetes in relation to intake of sugar-sweetened and artificially sweetened beverage and to explore how it relates to markers of insulin resistance, beta cell function and autoimmunity.

Subjects and methods

Study population and design

Analyses were based on data from the ESTRID study (Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes), a Swedish population-based case-control study initiated in 2010 (Supplementary Fig. 1, see section on supplementary data given at the end of this article) (21). ESTRID is a sub-study to ANDIS (All New Diabetics in Scania; http://andis.ludc.med.lu.se), which is a large study aiming to characterize all new diabetes cases within the county of Scania (southern Sweden, 1.3 million inhabitants) with regard to diabetes type, clinical features and genotype. LADA constitutes 5% of all diabetes in the ANDIS Registry, all ages included (22). All newly diagnosed cases of LADA identified in ANDIS since 2010 have been invited to participate in the ESTRID study, together with a random sample of incident type 2 diabetes cases in ANDIS (4:1 ratio to LADA cases). Since 2012, ESTRID has also recruited cases of LADA and type 2 diabetes from ANDiU (All New Diabetics in Uppsala; http://www.andiu.se/), a study using the ANDIS setup but covering the county of Uppsala (in mid-Sweden, 350 000 inhabitants). The Swedish Population Register was used to select a random sample of controls who was free of diabetes, aged ≥35 years and matched to the cases based on participation date and county (incidence density sampling (23)) in a 6:1 ratio to LADA cases. A self-administered questionnaire including a large number of questions on health and lifestyle factors was sent by mail to all cases and controls. Participants included in this study were recruited in ESTRID between September 2010 and July 2015. The participation rate was 81% for cases and 66% for controls.

The current analysis excluded those with incomplete information on exposure ($n=26$) or any of the main covariates (family history of diabetes, education, physical activity, smoking, alcohol intake and BMI; $n=53$). We further excluded individuals with reported total daily energy intake that deviated more than 3 SD. from the $\log_e$-transformed sex-specific mean energy intake ($n=7$ women and $n=11$ men). After exclusions, 357 cases of LADA, 1136 cases of type 2 diabetes and 1371 controls remained for analysis (96% of included cases were recruited from ANDIS and 4% from ANDiU). Informed consent was provided by all participants. The study has been approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden.

Serological assays

C-peptide was measured by the Cobas e 601 analyzer (Roche Diagnostics) or IMMULITE 2000 (Siemens Healthcare Diagnostics Product). GADA was quantitatively determined using ELISA (enzyme immunoassay; RSR Limited, Cardiff, UK). ELISA gives a maximum value of 250 IU/mL and has a sensitivity of 84% and specificity of 98% for a cutoff level of 10.7 IU/mL (24).

Case definition

All diabetes cases were diagnosed by a physician within the regional health care system. Classification into diabetes subtype was based on fasting blood samples collected at the time of diagnosis. Criteria for LADA diagnosis were age ≥35 years, GADA positivity (≥10 IU/mL) and serum C-peptide exceeding the lower limit

for the normal range as specified by the manufacturer (≥0.2 nmol/L for IMMULITE and ≥0.3 nmol/L for Cobas). Type 2 diabetes criteria were ≥35 years, GADA negativity (<10 IU/mL) and C-peptide levels above >0.6 nmol/L (IMMULITE) or >0.72 nmol/L (Cobas). There are no unified criteria for LADA diagnosis and classification, but the criteria used in this study are in line with previous literature (19). The exception is C-peptide, which in this study is used as an indicator of remaining insulin production to separate LADA from type 1 diabetes. It replaces the insulin therapy criterion (i.e. no insulin therapy within 6–12 months of diagnosis) that is commonly used, but to some extent, open to subjectivity because it reflects the assessment made by the treating physician. Homeostatic Model Assessment for insulin resistance (HOMA-IR) and beta cell function (HOMA-B) were calculated based on fasting plasma glucose and C-peptide levels at diagnosis (25).

Dietary assessment

Information on sweetened beverage intake was obtained from a semi-quantitative Food Frequency Questionnaire (FFQ) consisting of 132 items. The participants were asked to report their habitual food intake during the preceding year. The cases were specifically instructed to report their average intake during the year before diagnosis. Four questions were asked about sweetened beverage intake: cola, other soft drinks/soda, diet cola and other diet soft drinks/soda. The participants were asked to report their average number of 200 mL servings per day or per week. 'Other soft drink/soda' also refers to other sweetened beverages such as nectars and diluted syrups. The FFQ includes a separate question on 100% fruit juice, which was not evaluated in this study.

Information on potentially confounding dietary factors was also derived from the FFQ. Nutritional data from the Swedish National Food Agency database were used to estimate the average daily intakes of total energy and nutrients based on the FFQ.

The FFQ has been validated against 24-h recall interviews (26), diet records (27) and dietary biomarkers (28). Validation of individual food items against four 1-week diet records in a subsample of 129 women indicated a correlation of 0.6 for FFQ-reported sweetened beverage intake (A Wolk, unpublished results). The FFQ-based nutrient estimates have been validated in comparison with the mean of fourteen 24-h recall interviews in 248 men, and showed Spearman correlation coefficients ranging from 0.44 (protein) to 0.81 (alcohol) (26).

Other covariate assessment

BMI at age 20 and at present was calculated based on self-reported height and weight. Education was assessed with a question of the highest attained level of education and categorized into elementary school, high school or university. Family history of diabetes was categorized as yes/no for any type of diabetes in first-degree relatives. Leisure time physical activity during the preceding year was assessed by a question with four response options ranging from sedentary to regularly active. Smoking habits were categorized as never smoker, former or current smoker. Estimated total alcohol intake was categorized into non-consumption, 0.01–4.9 g/day, 5.0–14.9 g/day and ≥15.0 g/day.

Statistical analysis

Conditional logistic regression model was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) of LADA and type 2 diabetes in relation to sweetened beverage intake. We analyzed not only the total intake but also performed separate analysis for sugar-sweetened and artificially sweetened beverages. One serving was defined as 200 mL, and exposure was assessed as continuous as wells as categorical (<1, 1–2 and >2 servings per day) with non-consumers as reference. ORs are presented after adjustment for age and sex (model 1), and with additional adjustment for education, family history, physical activity, smoking, alcohol intake, total energy intake (kcal/day) and the following dietary factors in grams per day: vegetables, fruit, whole grain, fatty fish, red/processed meat, biscuits/sweets/salty snacks and coffee (servings/day) (model 2). Current BMI was considered to potentially be in the causal pathway and was included separately in the model (model 3). Results of model 3 are presented in the text, unless otherwise specified. Stratified analyses were performed using BMI and GADA levels (LADA) respectively. Sensitivity analyses included restricting the analysis to cases who participated within six months of diagnosis and to those not being on dietary treatment to minimize reverse causation. To investigate whether the association between highly sweetened beverage consumption and diabetes reflects increased thirst before diagnosis, we assessed the association between water consumption and risk of LADA/type 2 diabetes.

Because of the incidence density sampling design, the estimated ORs could be interpreted as incidence rate ratios (23). Two-sided P values were calculated using χ^2 (proportions) or Wilcoxon–Mann–Whitney test

(means and medians). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

Mean age was 58.8 years for LADA patients, 63.2 years for type 2 diabetes patients and 58.5 years for controls (Table 1). Patients with LADA had lower BMI and were less insulin resistant, but had worse beta cell function and were more often treated with insulin after diagnoses compared with type 2 diabetes patients. Family history of diabetes was almost as common in LADA (45%) as in type 2 diabetes (50%), but less frequent among controls (24%). Median diabetes duration on the date of participation was 7.5 months for LADA and 5.3 months for type 2 diabetes (data not shown in table).

Lifestyle characteristics by category of sweetened beverage consumption

The proportion of participants (irrespective of case/control status) who were non-consumers of both sugar-sweetened and artificially sweetened beverages was 63%. High consumers of total sweetened beverages (>2 servings per day of sugar-sweetened beverages and artificially sweetened beverages) had considerably higher BMI than other consumers and the largest annual weight gain (1.05% vs 0.72% in non-consumers) since age 20 (Table 2). In addition, they had generally less favorable lifestyle compared with those consuming little or no sweetened beverages, including higher prevalence of smoking, low physical activity, lower consumption of vegetables, fruit, fatty fish and whole grains and higher consumption of red/processed meat and biscuits/sweets/salty snacks. Comparing high consumers of sugar-sweetened vs artificially sweetened beverages suggests that the latter group reported lower total energy intake but tended to have higher BMI both at present and at age 20 (Supplementary Table 1).

LADA and sweetened beverage consumption

The risk of LADA was increased 2-fold (OR: 1.99, 95% CI: 1.11–3.56) for the group consuming more than two servings of sweetened beverages per day compared with non-consumers (Table 3), whereas no excess risk was seen in consumers of up to two servings per day. At consumption levels exceeding five servings per day (7 cases/6 controls), an OR of 4.47 (95% CI: 1.21–16.47) was observed. Each increment of daily serving conferred a 15% increased risk (OR: 1.15, 95% CI: 1.02–1.29). The results were similar in a more refined analysis of sugar-sweetened and artificially sweetened beverage intake separately, with an OR of 1.18 (95% CI: 1.00–1.39) and OR of 1.12, (95% CI: 0.95–1.32) respectively, per daily serving.

Stratifying the analyses by sex, age, family history of diabetes, BMI and median GADA levels (191 IU/mL) of the LADA patients indicated that the excess risk in high consumers of sweetened beverages was consistent across most subgroups (Supplementary Fig. 2). However, the increased risk of LADA was primarily seen in men, but analysis of women was based on a very limited number of high consumers (6 cases/19 controls).

Table 1 Characteristics of LADA and type 2 diabetes cases from ANDIS/ANDiU and controls participating in ESTRID, 2010–2015. Data are presented as mean (S.D.) unless otherwise stated.

	Controls	LADA	Type 2 diabetes	*P*[a]
n	1371	357	1136	
Age (years)	58.5 (13.3)	58.8 (12.5)	63.2 (10.3)	<0.0001
Sex (% women)	53	47	40	0.0117
BMI (kg/m^2)	25.9 (4.0)	28.2 (5.4)	31.1 (5.4)	<0.0001
Overweight (BMI ≥25) (%)	54	71	93	<0.0001
Obese (BMI ≥30) (%)	14	32	51	<0.0001
Family history of diabetes (% yes)	24	45	50	0.0813
Insulin treatment (%)[b]	–	42	6	<0.0001
Metformin and/or sulfonylurea treatment (%)[b]	–	55	62	0.0198
HOMA-IR, median (interquartile range)[b]	–	2.7 (1.8–4.4)	3.5 (2.7–4.9)	<0.0001
HOMA-B, median (interquartile range)[b]	–	39 (14–69)	68 (42–92)	<0.0001
GADA, median (interquartile range) (IU/mL)	–	191 (27–250)	–	–

[a]*P* for difference between LADA and type 2 diabetes. [b]The information is only available for LADA and type 2 diabetes patients.

Type 2 diabetes and sweetened beverage consumption

The OR of type 2 diabetes was increased by 2.39 (95% CI: 1.39–4.09) in those consuming more than two servings of sweetened beverages per day compared with non-consumers (Table 3). Consumption of more than five servings per day (18 cases/6 controls) was associated with an OR of 10.53 (95% CI: 2.75–40.33). The risk of type 2 diabetes was increased by 20% for each daily serving increment (OR: 1.20, 95% CI: 1.07–1.34). Similar findings were seen when assessing sugar-sweetened (OR: 1.21, 95% CI: 1.05–1.41) and artificially sweetened beverages (OR: 1.18, 95% CI: 1.01–1.38) separately. The excess risk in high consumers was seen across subgroups of sex, age, family history of diabetes and BMI (Supplementary Fig. 3).

HOMA-IR, HOMA-B and GADA

Median HOMA-IR tended to be higher among high consumers of sweetened beverages (>2 servings per day) compared with that among non-consumers for LADA (3.7 vs 2.5, $P=0.0561$), and more clearly shown for type 2 diabetes patients (4.5 vs 3.5, $P=0.0002$). In contrast, there was a tendency of lower HOMA-B levels among high consumers compared with that among non-consumers in the LADA patient group (20 vs 48, $P=0.0588$ for median). This difference was more pronounced among type 2 diabetes patients (55 vs 70, $P=0.0378$). No difference in GADA levels was observed in high consumers compared with that in non-consumers (250 vs 204, $P=0.6511$) among LADA patients.

Sensitivity analyses

The results were unchanged when using occupation instead of education as an indicator for socioeconomic status. Sensitivity analysis conducted to explore reverse causation indicated similar results; when restricting the analysis to patients responding to the questionnaire within six months of diagnosis, the excess risk among high (>2 servings per day) consumers persisted for both LADA (OR: 2.74, 95% CI: 1.16–6.47) and type 2 diabetes (OR: 2.02, 95% CI: 1.09–3.74). For type 2 diabetes in which we had larger number of cases, we could further restrict the analysis to cases responding within three months and observed a similar association (OR: 3.18, 95% CI: 1.13–8.95). Exclusion of patients reporting that they were on dietary treatment while filling out the questionnaire indicated similar results for LADA (OR: 2.01, 95% CI: 1.07–3.78) and type 2 diabetes (OR: 2.15, 95% CI: 1.21–3.83).

Table 2 Characteristics of participants in ESTRID by intake of sweetened beverages. Data are presented as mean (s.d.) unless otherwise stated.

	Total sweetened beverage intake (no. of 200 mL servings/day)				
	0	<1	1–2	>2	*P*
Mean intake (g/day)	0	76	287	890	(Highest vs lowest)
n (%)	1815 (63)	587 (20)	302 (11)	160 (6)	
Sugar-sweetened beverage (g/day)	0 (0)	46 (44)	148 (146)	461 (676)	<0.0001
Artificially sweetened beverage (g/day)	0 (0)	30 (44)	139 (153)	429 (424)	<0.0001
Age (years)	63.0 (11.4)	55.2 (11.8)	58.6 (13.6)	52.6 (11.6)	<0.0001
Sex (% women)	50	46	38	33	<0.0001
High level of education (% university)	29	31	22	14	<0.0001
BMI current (kg/m^2)	27.8 (5.1)	28.4 (5.7)	29.1 (5.1)	30.8 (6.9)	<0.0001
BMI at age 20 (kg/m^2)[a]	21.7 (3.1)	22.0 (3.5)	22.4 (3.2)	23.3 (4.0)	<0.0001
Average yearly weight gain (%) since age 20[a]	0.72 (0.62)	0.88 (0.77)	0.89 (0.74)	1.05 (0.82)	<0.0001
Physically inactive (%)	16	17	26	30	<0.0001
Family history of diabetes (% yes)	37	39	31	42	0.1793
Smoking status (% current)	18	22	26	34	<0.0001
Alcohol (g/day)	8.8 (9.8)	8.8 (9.4)	7.5 (10.2)	6.9 (9.1)	0.0049
Coffee (servings/day)	3.2 (2.3)	3.2 (2.2)	2.9 (2.3)	2.7 (2.4)	0.0043
Vegetables (g/day)	218 (146)	205 (115)	196 (159)	157 (110)	<0.0001
Fruits (g/day)	162 (128)	146 (112)	153 (124)	115 (116)	<0.0001
Red or processed meat (g/day)	87 (51)	102 (52)	107 (65)	118 (63)	<0.0001
Fatty fish (g/day)	22 (20)	20 (19)	21 (17)	16 (14)	<0.0001
Whole grain (g/day)	56 (34)	51 (30)	52 (32)	45 (33)	<0.0001
Biscuits, sweets, and salty snacks (g/day)	31 (26)	42 (30)	45 (32)	50 (38)	<0.0001
Energy (kcal/day)	1762 (557)	1900 (627)	2129 (766)	2236 (785)	<0.0001

[a]Missing for 19% of participants.

Table 3 Odds ratios and 95% CIs of LADA and type 2 diabetes in relation to intake of sweetened beverages (sugar sweetened, artificially sweetened and total).

	LADA				Type 2 diabetes			
		Consumers (no. of 200 mL servings/day)				Consumers (no. of 200 mL servings/day)		
	Non-consumers	<1	1–2	>2	Non-consumers	<1	1–2	>2
Sugar-sweetened beverage								
Cases/controls	268/1029	53/239	26/85	18-Oct	896/1029	130/239	66/85	44/18
Model 1	1	0.88 (0.63–1.24)	1.16 (0.72–1.84)	1.94 (0.87–4.32)	1	0.76 (0.59–0.98)	0.94 (0.66–1.35)	3.81 (2.07–7.00)
Model 2	1	0.95 (0.66–1.35)	1.15 (0.69–1.91)	2.11 (0.87–5.12)	1	0.75 (0.56–1.00)	0.84 (0.56–1.24)	3.45 (1.74–6.83)
Model 3	1	0.95 (0.66–1.36)	1.02 (0.61–1.71)	2.20 (0.90–5.36)	1	0.75 (0.55–1.03)	0.68 (0.44–1.05)	3.17 (1.45–6.93)
Model 3 (continuous)	1	1.18 (1.00–1.39) per 200 mL serving/day			1	1.21 (1.05–1.41) per 200 mL serving/day		
Artificially sweetened beverage								
Cases/controls	289/1151	34/121	20/75	14/24	926/1151	110/121	58/75	42/24
Model 1	1	1.16 (0.77–1.75)	1.13 (0.67–1.90)	2.47 (1.24–4.90)	1	1.61 (1.19–2.18)	1.27 (0.86–1.86)	4.41 (2.48–7.82)
Model 2	1	1.10 (0.71–1.69)	1.06 (0.62–1.82)	2.06 (1.01–4.20)	1	1.53 (1.09–2.14)	1.16 (0.76–1.79)	3.54 (1.91–6.54)
Model 3	1	1.04 (0.67–1.62)	0.92 (0.53–1.61)	1.90 (0.91–3.97)	1	1.47 (1.00–2.14)	0.86 (0.53–1.39)	2.42 (1.19–4.92)
Model 3 (continuous)	1	1.12 (0.95–1.32) per 200 mL serving/day			1	1.18 (1.01–1.38) per 200 mL serving/day		
Total sweetened beverage								
Cases/controls	213/880	79/297	40/147	25/47	722/880	211/297	115/147	88/47
Model 1	1	1.17 (0.86–1.58)	1.17 (0.80–1.73)	2.30 (1.36–3.91)	1	1.17 (0.94–1.47)	1.21 (0.91–1.61)	4.12 (2.69–6.29)
Model 2	1	1.17 (0.85–1.61)	1.19 (0.78–1.81)	2.12 (1.20–3.75)	1	1.11 (0.86–1.42)	1.10 (0.80–1.51)	3.31 (2.07–5.31)
Model 3	1	1.13 (0.82–1.56)	1.02 (0.66–1.56)	1.99 (1.11–3.56)	1	1.05 (0.79–1.39)	0.79 (0.55–1.13)	2.39 (1.39–4.09)
Model 3 (continuous)	1	1.15 (1.02–1.29) per 200 mL serving/day			1	1.20 (1.07–1.34) per 200 mL serving/day		

Cases/controls indicate how the total number of LADA cases ($n=357$), type 2 diabetes cases ($n=1136$) and controls ($n=1371$) were distributed between the four categories of intake.
Model 1: Age and sex. Model 2: Model 1 + education, family history of diabetes, physical activity, smoking, alcohol, coffee, vegetables, fruit, red/processed meat, fatty fish, snacks, wholegrain, total energy intake + mutual adjustment for sugar-sweetened/artificially sweetened beverages. Model 3: Model 2 + BMI.

Finally, there was no association between water consumption (as an indicator of excessive thirst during the year before diagnosis caused by hyperglycemia) and risk of neither LADA (OR: 0.98, 95% CI: 0.94–1.02 per daily serving) nor type 2 diabetes (OR: 0.99, 95% CI: 0.96–1.03).

Discussion

High intake of sweetened beverages was associated with an increased risk of LADA; a two-fold increased risk was seen in consumers of more than two 200 mL servings per day, and each daily serving increment in sweetened beverage intake conferred a 15% increased risk. High consumers also experienced a two-fold increased risk of type 2 diabetes and a 20% risk increase per serving, which is consistent with findings in a recent meta-analysis of prospective data (7). The associations were similar in separate analyses of sugar-sweetened and artificially sweetened beverages for the risk of LADA as well as type 2 diabetes, which has also been previously suggested for type 2 diabetes (8).

Proposed mechanisms by which sugar-sweetened beverage intake may increase diabetes risk are predominantly related to induced insulin resistance (29) and include decrease in hepatic insulin sensitivity (30), adverse effects of increased insulin demand due to high intermittent spikes in blood glucose levels (16) and increase in inflammatory markers such as C-reactive protein (31). Another possibility is that the increased risk is mediated by increases in overweight (32). In line with previous studies on type 2 diabetes (1, 3, 5, 7, 8), the observed positive association remained after adjustment for BMI, possibly suggesting a direct adverse effect of sweetened beverage intake on glucose homeostasis. However, it could be that the BMI does not fully indicate the level of visceral fat, which is a predictor of type 2 diabetes (33). An effect on the development of autoimmunity is also possible. Sugar-sweetened beverages have previously been linked to type 1 diabetes (13) as well as rheumatoid arthritis (34), with suggestions of sugar being involved in causing infections and/or inflammation (34). In this study, high consumption of sweetened beverages was associated with insulin resistance and low beta cell function in type 2 diabetes patients, with similar tendencies in LADA, whereas no association with GADA levels was observed. A link between sugar-sweetened beverage intake and HOMA-IR was previously reported in adolescents (35, 36). Hence, the most plausible explanation may be that the excess risk of LADA among high consumers of sweetened beverages is related to mechanisms involving insulin resistance or other pathophysiological features shared with type 2 diabetes. The findings are also supportive of the accelerator hypothesis, in which it is postulated that beta cell stress caused by insulin resistance activates the immune system and consequently accelerates beta cell apoptosis leading to manifest diabetes. The intensity of the immune response, and hence the tempo of beta cell destruction, is suggested to be modulated by genetic susceptibility conferred by HLA genes (37).

We also found an excess risk in high consumers of artificially sweetened beverages, which is in line with previous studies in type 2 diabetes (1, 7). Although not containing sugars and thus not contributing to caloric intake, it has been suggested that artificially sweetened beverages may stimulate appetite, which may lead to positive energy balance and weight gain (38). Further, artificial sweeteners have also been hypothesized to have adverse effects on abdominal fat (39) and gut microbiota (12), which may induce glucose intolerance. Alternatively, one could speculate that consumers of artificially sweetened beverages may have swapped from sugar-sweetened beverages to prevent further weight gain (39). In that case, we may actually be assessing diabetes risk related to previous high consumption of sugar-sweetened beverages. In line with this explanation, we found the highest BMI, both at present and age 20, in the group reporting high intakes of artificially sweetened beverages.

The main strength of this study is the population-based design, with a large number of incident LADA patients, and the use of a FFQ that has been thoroughly validated against both biomarkers (28) and 24-h recall interviews (26), together with information on a wide variety of potential confounding factors. For sweetened beverage intake, correlation with diet records showed good agreement (A Wolk, unpublished results), but unfortunately there is no biomarker of such intake. Validation of the FFQ questions has been performed in another setting, and a number of years ago, however, the validation studies included both men and women who were all within the same age range as participants of this study.

The main limitation is the retrospective design that may lead to recall bias. However, for a rare disease like LADA, the case–control design is far more efficient than the corresponding prospective study, which would have required an unrealistically large sample and/or follow-up time to yield the same number of cases. In this study, patients were meticulously instructed to report their dietary habits as they were before diabetes diagnosis, but some patients may have reduced their

consumption of sweetened beverages since diagnosis and report accordingly. Still, this would not lead us to overestimate the risk in high consumers, but rather the opposite. The fact that the patients were asked to recall their consumption of sweetened beverages as they were before diagnosis, whereas the controls were asked to recall their intake during the year directly before participation date, may introduce bias. In an attempt to minimize such recall bias, analysis were run separately for patients filling out the questionnaire within six months and three months of diagnosis, and excluded those who were treated by diet modification, but the results were similar. Some controls may have undiagnosed diabetes. This would make controls more similar to the cases with regard to lifestyle and hence dilute the true associations between intake of sweetened beverages and diabetes risk. Bias would be introduced if the participating controls are not representative of the population generating the cases, i.e. inhabitants of the counties of Scania and Uppsala, with regard to both sweetened beverage intake and other covariates. In a comparison using data of the general population, we found that the participating controls are equivalent with regard to educational level (data from Statistics Sweden, www.scb.se).

One could also speculate that the high consumption of sweetened beverages reported by patients reflects greater thirst in the period preceding diagnosis due to hyperglycemia. This is difficult to assess, but we noted that these patients did not report excess intake of water. Finally and most importantly for the credibility of these findings with regard to type 2 diabetes, our results were in line with previous reports based on prospective data with diet reported a several years before diagnosis (1, 3). False-positive LADA patients, i.e. truly type 2 diabetes (i.e. GADA negative) patients, but misclassified as LADA, could drive the results for LADA in the same direction as that of type 2 diabetes. However, this is unlikely to fully explain the observed association for LADA considering the high specificity of the GADA assay and the fact that the same magnitude of association was also observed among LADA patients with high GADA levels. Another explanation for our findings could be that high intake of sweetened beverages simply is a marker of an overall poor lifestyle leading onto the trajectory toward diabetes onset. We did observe that high consumers had an unhealthier lifestyle in general, and the highest BMI, both currently and at age 20, and the greatest weight gain since age 20. The excess risk in high consumers did persist after adjustment for a wide range of dietary and lifestyle factors including BMI, but we cannot rule out residual confounding due to unmeasured or imprecisely measured factors, such as BMI, energy intake or socio-demographic factors, as an explanation for our results. The group of high consumers constitutes 6% of the study participants, but it is noteworthy that among participants below age 50, 12% consume such high levels.

In conclusion, these findings add support to the accumulating evidence suggesting that high intake of sweetened beverages, both sugar-sweetened and artificially sweetened, is a potential risk factor for type 2 diabetes. Importantly, these findings indicate that the adverse health effects seen with high sweetened beverage intake also encompass autoimmune forms of diabetes. The excess risk seems not to be fully explained by caloric intake or BMI, opening up for other explanations possibly including direct adverse effects of sweetened beverages on glucose homeostasis and insulin sensitivity. The suggested positive association between artificially sweetened beverages and diabetes risk remains to be further explored. This study supports the notion that dietary factors may influence LADA development (21, 40, 41). This is important as the identification of modifiable risk factors could aid in preventing autoimmune diabetes. It is especially urgent in times when diabetes prevalence is on the rise (42) and sweetened beverage consumption continues to be high (43).

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-16-0376.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

J E L contributed to the design of the study, analyzed and interpreted the data and wrote the manuscript. S C researched data, contributed to the design of the study, interpreted the data and reviewed and revised the manuscript. T A contributed to data analysis, interpretation of data and reviewing and revising of the manuscript. P-O C, M D, L G and M M researched data and contributed to reviewing and revising of the manuscript. T T and A W contributed to interpretation of data

and reviewing and revising of the manuscript. All authors have read and approved the final version of the manuscript. J E L is the guarantor of the study taking responsibility for the integrity of the data and affirming that this is a truthful report of the study.

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