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Sugar-sweetened beverages, low/no-calorie beverages, fruit juices intake and risks of metabolic syndrome in adults: The SWEET project

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ABSTRACT

Background and aims: Metabolic syndrome (MetS) is an important determinant of cardiometabolic disease development, with excessive sugar intake as one of the key modifiable risk factors. However, evidence on the association between sugar-sweetened beverages (SSB), their replacement by low/no caloric beverages (LNCB), and MetS development is still limited.

Methods and results: Data from participants' of Lifelines (n = 58 220), NQPlus (n = 1094) and Feel4Diabetes (n = 342) were prospectively analysed. Dose-response associations were investigated using restricted cubic spline analyses (Lifelines). Cox proportional hazard regression analysis with robust variance was used to quantify associations between intakes of SSB, fruit juices (FJ) and LNCB and MetS incidence; data were pooled using random-effects models. Associations were adjusted for demographic, lifestyle and other dietary factors. In Lifelines, NQPlus, and Feel4Diabetes, 3853 (7 %), 47 (4 %), and 39 (11 %) participants developed MetS, respectively. Pooled analyses showed that each additional serving of SSB was associated with a 6 % higher risk of MetS (95%CI 1.02–1.10). A J-shaped association was observed for FJ and MetS, with a significant inverse association at moderate intake levels (IPR 0.89, 95 % CI 0.82–0.96). LNCB intake was not associated with MetS (IPR 1.59, 95%CI 0.74–2.43), but findings across studies were inconsistent (I^2 94 %, *p-value* <0.01). Replacing SSB with FJ or LNCB did not show any associations with MetS incidence.

Conclusion: SSB intake was adversely associated with MetS incidence. A J-shaped association was observed between FJ and MetS. For LNCB, results were inconsistent across studies and therefore findings must be interpreted cautiously.

1. Introduction

Globally, about 13–31 % of adults, 3 % of children, and 5 % of adolescents are affected by Metabolic Syndrome (MetS) [1,2]. MetS is a biologically complex condition characterized by abdominal obesity, dyslipidaemia, hypertension, and impaired glucose metabolism [3], which are important risk factors for cardiometabolic disease development including type 2 diabetes (T2D) and cardiovascular disease (CVD) [4–7]. Obesity, sedentary lifestyle and unhealthy diet, including excessive sugar intake, are well-known modifiable risk factors of MetS [3,8].

Accordingly, various health authorities have already successfully

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Acronyms:

AQuAA	Activity Questionnaire for Adults and Adolescents
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
DBP	diastolic blood pressure
FFQs	food frequency questionnaires
FJ	fruit juices
FPG	fasting plasma glucose
HDLc	high-density lipoprotein cholesterol
IPAQ	Physical Activity Questionnaire
IPR	incidence proportion ratios
IQR	interquartile range
LNCB	low/no calorie beverages
MET	metabolic equivalent
MetS	metabolic syndrome
NQPlus	Nutrition Questionnaire Plus
SBP	systolic blood pressure
SD	standard deviation
SQUASH	Short Questionnaire to Assess Health
SSB	sugar-sweetened beverages
T2D	type 2 diabetes
TG	triglycerides

recommended limiting sugar intake [9,10] as shown by decreasing trends in sugar intake in the US [11,12]. However, consumption levels remain high and additional efforts are urgently needed [11,13,14]. Replacing sugars with low/no-caloric sweeteners may be an effective strategy to reduce sugar content in foods and beverages, and may aid a further reduction of sugar intake at a population level.

Based on various short-term trials, replacing sugar with low/no-caloric sweeteners to improve MetS parameters seems promising [15–17]. Yet, long-term observational studies are limited, and overall, do not support the findings of short-term trials [18–20]. This underscores the need for further research, particularly including epidemiological analyses within larger datasets for detailed insights. Therefore, we studied associations between sugar-sweetened beverages (SSB), fruit juices (FJ), and low/no caloric beverages (LNCB) intakes, and MetS incidence in three European population-based cohort studies, including well-powered stratified analyses as well as theoretical substitution analyses to examine whether replacing SSB by LNCB or FJ alters MetS risk.

2. Methods

2.1. Study design and population

The study was part of the SWEET project, an EU-funded initiative examining the risks and benefits of replacing sugar with sweeteners and sweetness enhancers (www.sweetproject.eu). For current analyses, data were sourced from the Lifelines Cohort (Lifelines) study (The Netherlands), Nutrition Questionnaire Plus (NQPlus) study (The Netherlands), and Feel4Diabetes-study (Feel4Diabetes; Greece) (Supplemental Table 1) [21–23]. Each study collected data based on its objectives and protocols, and variables of interest were harmonized for analysis. All studies were conducted according to the principle of the Declaration of Helsinki. All participants gave written informed consent before participating.

2.2. Lifelines

Lifelines is a multi-disciplinary prospective cohort study examining in a unique three-generation design the health and health-related behaviours of 167 729 persons living in the northern part of The Netherlands [21,24]. It employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to health and disease in general population. Between 2006 and 2013, people aged 0–93 years were recruited to undergo baseline measurements. People who had limited life expectancy (<5 years) due to severe psychiatric or physical illness or were unable to read Dutch were not invited to participate. Participants are followed for over 30 years, in which every one and a half years, participants are invited to complete a follow-up questionnaire. In addition, several physical measurements are conducted and additional questionnaires are administered on average every five years. For present analyses, data from 152 728 participants aged ≥18 years were included. After consecutive exclusion of those with missing dietary data (n = 8633), implausible energy intake (<800 or >4000 kcal/day for men or <500 or >3500 kcal/day for women) (n = 15 483) [25], missing outcome (n = 52 051), diagnosis of diabetes, CVD, or having MetS at baseline (n = 13 764), or missing covariates (n = 4577), n = 58 220 remained for current analyses (Supplemental Table 2). Lifelines has been approved by the Medical Ethical Review Committee of the University Medical Center in Groningen under number 2007/152.

2.3. NQPlus

NQPlus is a prospective cohort study involving Dutch adults aged 20–70 years from the central part of The Netherlands [22]. This study aimed to establish a national dietary reference database to develop and validate food frequency questionnaires (FFQs) as well as to investigate the potential long-term impact of dietary factors on health-related outcomes. Participants were recruited between 2011 and 2013, and those who were able to make their own decisions and had sufficient knowledge of the Dutch language (spoken and written) were eligible to participate. Participants were followed for 2 years, during which all measurements were repeated annually. In total, 2048 participants were included, of which 1647 provided dietary intake data. After consecutively excluding participants with implausible energy intake (n = 20), missing outcome data (n = 235) or having MetS, diabetes or CVD at baseline (n = 298), n = 1094 remained for current analyses. Due to the high proportion of missing covariates (9 %), multiple imputations were applied using “mice” package in R and five duplicate datasets were produced [26]. NQPlus was approved by the ethical committee of Wageningen University and Research.

2.4. Feel4Diabetes

Feel4Diabetes is a European Union-funded intervention study, focusing on T2D prevention by promoting healthy eating and lifestyle among vulnerable families across Europe. Feel4Diabetes was a cluster-randomized design with two components: 1) ‘all families’ via school settings, and 2) ‘high-risk families’ component carried out in families with increased risk of T2D via community health centres [23,27]. In 2016, participants from selected provinces in Belgium, Bulgaria, Finland, Greece, Hungary and Spain were included in baseline measurements. Participants were followed for 2 years, and data from 765 participants aged ≥18 years from Greece who belonged to ‘high-risk families’ were available for current analyses. After consecutively excluding participants with missing exposure data (n = 86), missing information on MetS at follow-up (n = 179), or having MetS and diabetes at baseline (n = 187), n = 342 participants were included in current analyses. Due to the high percentages of missing covariates (27 %), multiple imputations were applied with five duplicate datasets

produced [26]. Feel4Diabetes was approved by the Bioethics Committee of Harokopio University. Feel4Diabetes is registered with ClinicalTrials.gov (NCT02393872).

2.5. Dietary assessment

In all studies, dietary intake was assessed at baseline using FFQs. In Lifelines and NQplus, dietary intake data were collected using a validated 110-item FFQ [28] and a 183-item semi-quantitative FFQ [29,30], respectively. FFQs were used to collect information on intake frequency and portion sizes of all major food groups using the previous month as a reference period. Questions on intake frequency were answered by selecting responses ranging from "never" to "6–7 days/week". Intakes of energy and foods were calculated by multiplying intake frequency by portion size and nutrient content (grams) as indicated in The Dutch Food Composition Table (NEVO) (2011) [31]. In Feel4Diabetes, dietary intake was assessed using a 33-item FFQ covering major food groups, which was a modified version of the questionnaire for National Type 2 Diabetes Prevention in Finland (FIN-D2D) [32]. Questions were completed by selecting intake frequency and a pre-specified portion size based on common household units. Food intakes were calculated by multiplying intake frequency by portion size. When the frequency category was defined as a range, such as "3–4 servings/day", the median of the intake range (3.5 servings/day) was taken. When the category started or followed with "less than" or "more than" such as "more than 5 servings/day", the given portion size was assumed, which in this case was 5 servings/day. The FFQ used in Feel4Diabetes was not developed to derive intakes of energy and specific nutrients. In all included studies, SSB and LNCB were defined as soft drinks or lemonade, with or without added sugar, respectively. Water, coffee, or tea sweetened with sugar or sweeteners were not included. FJ was defined as apple juice, orange juice, or mixed fruit juice, mostly pasteurized, and included both 100 % juices and those with added sugars. Intake of SSB, FJ, and LNCB was reported in servings of 150 ml.

2.6. MetS ascertainment

Anthropometric assessments, including waist circumference, height, and weight were performed by well-trained staff according to each cohort's protocol. Participants were asked to remove shoes and heavy clothing, and empty their pockets before measurements. Waist circumference was measured to the nearest 0.5 cm in Lifelines and NQplus, and 0.1 cm in Feel4Diabetes. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). In all studies, blood samples were collected by trained staff after an overnight fast. Fasting plasma glucose (FPG) was analysed using standard procedures. Blood lipids including total cholesterol, high-density lipoprotein cholesterol (HDLc), and triglycerides (TG) were measured with enzymatic methods using routine procedures on a Roche Modular analyser (Roche, Basel, Switzerland) in Lifelines, Dimension Vista (Siemens, Erlangen, Germany) or a Roche Modular analyser (Roche Diagnostics, Indianapolis, USA) in NQplus, and Roche or Hitachi Modular analyser (Roche Diagnostics SA, Vasilia, Switzerland) in Feel4Diabetes. Blood pressure was measured using Dinamap PRO 100V2 in Lifelines, OMRON HEM-907 in NQplus, and OMRON M6 or M6 AC in Feel4Diabetes. Diagnosis of MetS was according to the harmonized criteria classification by International Diabetes Federation together with American Heart Association/National Heart, Lung, and Blood Institute ATPIII [3], with specific recommendations for FPG provided by European Diabetes Epidemiology Group [33]. Thus, MetS was defined as fulfilling at least three out of five criteria: (1) waist circumference $\geq$102 cm in men and $\geq$88 cm in women; (2) TG levels $\geq$1.70 mmol/L or used drug for elevated TG; (3) HDLc levels $<$1.03 mmol/L in men and $<$1.30 mmol/L in women; (4) systolic blood pressure (SBP) $\geq$130 mmHg and/or diastolic blood pressure (DBP) $\geq$85 mmHg or in antihypertensive drug treatment; (5) FPG level $\geq$6.1 mmol/L or used medication treatment of elevated glucose. Information on medication use at follow-up was not available in Lifelines. Thus, this information was not included in the outcome ascertainment.

2.7. Covariates

Information on sociodemographic, lifestyle, and disease history was obtained by self- or interviewer-administered questionnaires. Educational level was categorized into low, medium or high. Smoking status was categorized as a non-smoker, former, or current smoker. Physical activity and sedentary behaviours (i.e. TV-watching and/or sitting) were assessed using the Short Questionnaire to Assess Health (SQUASH) in Lifelines [34] and the Activity Questionnaire for Adults and Adolescents (AQuAA) in NQplus [35]. In Feel4diabetes, physical activity was assessed using a modified version of the International Physical Activity Questionnaire (IPAQ) [36]. Physical activity was reported in Metabolic equivalent (MET)-minutes per week for moderate-level activity and in minutes per week for sedentary behaviour. Alcohol intake (ethanol) was quantified using FFQ and was categorized as 0, $>$0-$\leq$10, $>$10-$\leq$20, or $>$20 g/day. No data on ethanol intake was available in Feel4Diabetes.

2.8. Statistical analysis

Baseline characteristics were presented as means with standard deviations for normally distributed continuous variables or as medians and interquartile ranges for skewed variables. Categorical variables were shown as numbers and percentages. First, dose-response associations between SSB, FJ and LNCB intakes and Mets risk were analysed using restricted cubic spline analyses (3 knots) [37]. The fit of the spline model was examined against a linear model with the likelihood-ratio test. To ensure adequate power and precision, restricted cubic spline analyses were only conducted in Lifelines. Cox proportional hazard regression with robust variance estimate was used to investigate associations of SSB, FJ and LNCB intakes with MetS risk resulting in Incidence Proportion Ratios [IPR] with a 95 % confidence interval [95%CI]) for each cohort. Theoretical substitution analyses were conducted using the leave-one-out model where the model included SSB, FJ and LNCB (servings/day) as one variable followed by beverage defined as a replacement. Subsequently, IPRs of individual cohorts were pooled using random-effects models, in which heterogeneity was also examined. The sample size of Lifelines also allowed us to conduct well-powered sensitivity analyses by adding adjustments for BMI or excluding participants with a desire to lose weight. Moreover, to assess for potential influence of residual confounders, the E-value was calculated for the Lifelines data [38]. All analyses were adjusted for age, sex (Model 1), educational level (low, medium, or high), moderate physical activity (MET-min/week), sedentary behaviour (min/week), smoking status (never, former, or current smoker), and alcohol use (0, $>$0-$\leq$10, $>$10-$\leq$20, or $>$20 g/d) if available (Model 2), other food intake groups including grains (g/d), potatoes (g/d), fats and oils (g/d), vegetables (g/d), fruits (g/d), meat (g/d), dairy (g/d), coffee (ml/d), tea (ml/d), legumes (g/d), nuts (g/d), sugary foods (g/d), and mutual adjustment for other beverages (SSB, FJ or LNCB in g/d), total energy intake (kcal/d) if available (Model 3). Statistical analyses were performed using R 4.0.2 and Rstudio 2022.02.0 for Lifelines and Rstudio 2022.07.0 for NQplus and Feel4Diabetes.

3. Results

More than half of the participants in Lifelines (62 %) and Feel4Diabetes (62 %) were women, whereas women and men were equally represented in NQPlus (51 %). Mean $\pm$ SD age ranged from 43 $\pm$ 6 in Feel4Diabetes to 53 $\pm$ 11 years in NQplus (Table 1). Most participants did not smoke at baseline (83 % in Lifelines, 93 % in NQplus and 67 % in Feel4Diabetes) and had a moderate education level (64 % in Lifelines and 57 % in Feel4Diabetes), except in NQPlus where most participants

Table 1
General characteristics of Lifelines, NQPlus, and Feel4Diabetes participants.

Characteristics[a]	Lifelines	NQPlus[b]	Feel4Diabetes[c]
N	58220	1094	342
Age, *years*	45 ± 12	53 ± 11	43 ± 6
Women, *n(%)*	35820 (62)	559 (51)	213 (62)
Education, *n(%)*			
Low	2019 (3)	8 (1)	24 (7)
Moderate	37046 (64)	457 (42)	196 (57)
High	19155 (33)	629 (57)	122 (36)
Smoking status, *n(%)*			
Never	28254 (49)	577 (55)	143 (42)
Former	19706 (34)	400 (38)	84 (25)
Current	10260 (17)	68 (7)	115 (33)
Moderate physical activity, *MET-min/week*	1665 [820, 2940]	825 [228, 1680]	60 [0, 225]
Sedentary behaviour, *min/week*	840 [630, 1260]	1800 [1200, 2640]	1680 [840, 3360]
Alcohol use, *n(%)*			
0 g/day	1267 (3)	43 (4)	NA
>0-≤10 g/day	41968 (72)	619 (57)	
>10-≤20 g/day	11240 (19)	224 (20)	
>20 g/day	3745 (6)	208 (19)	
Metabolic markers			
BMI, kg/m^2	25.3 ± 3.7	24.9 ± 3.3	27.4 ± 4.7
BMI≥25, *n(%)*	28459 (49)	501 (46)	226 (66)
TG, *mmol/l*	1.0 ± 0.5	1.0 ± 0.4	0.9 ± 0.4
HDLc, *mmol/l*	1.6 ± 0.4	1.7 ± 0.4	1.4 ± 0.4
SBP, *mmHg*	124 ± 15	124 ± 15	109 ± 14
DBP, *mmHg*	73 ± 9	73 ± 10	71 ± 9
FPG, *mmol/l*	4.9 ± 0.5	5.3 ± 0.5	5.3 ± 0.4
Waist circumference, *cm*	87.9 ± 10.9	88.4 ± 10.6	91.3 ± 12.5
Dietary intakes			
SSB, *serving/day*	0.1 [0.0, 0.6]	0.0 [0.0, 0.1]	0.0 [0.0, 0.2]
FJ, *serving/day*	0.2 [0.0, 0.6]	0.2 [0.0, 0.6]	0.2 [0.0, 0.7]
LNCB, *serving/day*	0.1 [0.0, 0.5]	0.0 [0.0, 0.0]	0.0 [0.0, 0.2]
Total energy, *kcal/d*	2045 ± 563	2068 ± 564	NA
Grains, *g/d*	181 [138, 234]	190 [139, 248]	120 [60, 310]
Potatoes, *g/d*	88 [55, 111]	61 [37, 95]	NA
Vegetables, *g/d*	105 ± 58	161 ± 87	271 ± 284
Fruits, *g/d*	110 [42, 220]	214 [86, 239]	71 [19, 135]
Meat, *g/d*	75 [55, 98]	66 [36, 92]	94 [71, 141]
Dairy, *g/d*	297 ± 180	305 ± 185	212 ± 265
Coffee, *ml/d*	418 ± 272	445 ± 298	346 ± 246
Tea, *ml/d*	232 [54, 348]	174 [67, 406]	0 [0, 36]
Nuts, *g/d*	8 [3,17]	12 [6, 23]	6 [2, 6]
Legumes, *g/d*	11 [0, 29]	38 [21, 78]	57 [43, 114]
Fats and oils, g/d	23 ± 16	26 ± 17	NA
Sugary foods, *g/d*	73 [46, 108]	49 [31, 79]	20 [11, 28]

Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; FJ, fruit juice; FPG, fasting plasma glucose; HDLc, high density lipoprotein cholesterol; LNCB, low/no-calorie sweetened beverages; MET, metabolic task equivalent; SBB, sugar-sweetened beverages; SBP, systolic blood pressure; TG, triglycerides.

[a] Values are mean ± SD, median [25th, 75th percentiles], or n (%) as indicated.

[b] n missing physical activity = 61, n missing sedentary activity = 61, n missing smoking status = 49.

[c] n missing physical activity = 7, n missing sedentary activity = 50, n missing vegetables = 3, n missing fruits = 3, n missing meat = 16, n missing coffee = 6, n missing tea = 11, n missing legumes = 10.

were highly educated (57 %). Median (IQR) SSB intake ranged from 0.0 (0.0–0.1) servings/day in NQPlus to 0.1 (0.0–0.6) servings/day in Lifelines. Similar intake levels were observed for LNCB. For FJ, median (IQR) intakes were similar in all cohorts (0.2 [0.0–0.6] in Lifelines and NQPlus and 0.2 [0.0–0.7] in Feel4Diabetes). Almost half of Lifelines' and NQPlus' participants had BMI≥25 kg/m^2 (49 % and 46 %), whereas a higher prevalence was observed in Feel4Diabetes (66 %). Mean ± SD of TG and DBP were rather comparable across cohorts (TG 1.0 ± 0.5, 1.0 ± 0.4, 0.9 ± 0.4 mmol/L and DBP 73 ± 9, 73 ± 10, and 71 ± 9 mmHg for Lifelines, NQPlus, Feel4Diabetes, respectively). For HDLc and SBP, mean ± SD were higher in Lifelines and NQPlus (HDLc 1.6 ± 0.4 and 1.7 ± 0.4 mmol/L and SBP 124 ± 15 mmHg in both cohorts) compared to Feel4Diabetes (HDLc 1.4 ± 0.4 mmol/L and SBP 109 ± 14 mmHg). For FPG, lower mean ± SD was observed in Lifelines (4.9 ± 0.5 mmol/L) than in NQPlus and Feel4Diabetes (5.3 ± 0.5 and 5.3 ± 0.4 mmol/L). In total, 3853 (7 %), 47 (4 %), and 39 (11 %) participants of Lifelines, NQPlus and Feel4Diabetes developed MetS during a follow-up time of ~4 years in Lifelines and 1–2 years in NQPlus and Feel4Diabetes (Table 2).

Dose-response analysis in Lifelines did not provide strong evidence of a non-linear association between SSB and MetS (*p non-linearity* = 0.09) (Fig. 1). Pooled results of all cohorts showed that each additional serving/day of SSB intake was associated with a 12 % higher risk of developing MetS (95%CI 1.08–1.16) after adjustment for age and sex (Table 2). The association attenuated but remained statistically significant after additional adjustment for other demographic, lifestyle and dietary factors (IPR 1.06, 95%CI 1.02–1.10); no interaction with sex or BMI was observed (p = 0.08 and 0.18, respectively) (Supplemental Table 3). Sensitivity analyses in Lifelines either controlling for BMI in the model or excluding those who had a desire to lose weight did not substantially alter the associations (Supplemental Table 4). Additional analyses on each MetS parameter in Lifelines, in general, confirmed the main finding (Supplemental Table 5).

Dose-response analysis provided strong evidence for a non-linear association between FJ intake and MetS (*p non-linearity* = 0.006) in Lifelines (Fig. 1). Analysis by intake categories indicated an inverse association with MetS incidence for intake level of <7 servings/week when compared to no intake, after adjustment for demographic and

Table 2
Adjusted associations of SSB, FJ, and LNCB intakes with MetS for each serving (150 ml) per day increment in participants of all cohorts.

	IPR (95%CI)			Pooled	
	Lifelines	NQPlus[a]	Feel4Diabetes[a]	IPR (95%CI)	I^2, *p value*
N total/ N(%) cases	58220/ 3853 (6.6)	1094/47 (4.3)	342/39 (11.4)		
SSB					
Model 1	1.12 (1.08–1.16)	0.86 (0.38–1.92)	1.11 (0.58–2.12)	**1.12 (1.08–1.16)**	0 %, 0.82
Model 2	1.06 (1.03–1.10)	0.83 (0.40–1.73)	1.01 (0.56–1.81)	**1.06 (1.03–1.09)**	0 %, 0.82
Model 3	1.06 (1.02–1.10)	0.74 (0.31–1.77)	1.26 (0.71–2.21)	**1.06 (1.02–1.10)**	0 %, 0.61
FJ					
Model 1	1.05 (1.00–1.11)	0.99 (0.66–1.49)	0.67 (0.30–1.49)	**1.05 (1.00–1.10)**	0 %, 0.63
Model 2	1.06 (1.00–1.11)	1.02 (0.70–1.49)	0.67 (0.31–1.45)	**1.06 (1.00–1.11)**	0 %, 0.60
Model 3	1.05 (0.99–1.10)	1.07 (0.70–1.63)	0.54 (0.22–1.31)	**1.05 (1.00–1.10)**	0 %, 0.53
LNCB					
Model 1	1.22 (1.19–1.25)	1.17 (0.80–1.72)	1.80 (1.28–2.53)	**1.38 (1.01–1.76)**	82 %, <0.01
Model 2	1.19 (1.16–1.22)	1.14 (0.75–1.75)	1.90 (1.37–2.63)	**1.41 (0.93–1.88)**	89 %, <0.01
Model 3	1.17 (1.14–1.21)	1.16 (0.78–1.74)	2.48 (1.60–3.86)	**1.59 (0.74–2.43)**	94 %, <0.01

Model 1: adjusted for age and sex.
Model 2: model 1 + education background, moderate physical activity, sedentary behaviour, smoking status, alcohol intake.
Model 3: model 2 + grains, potatoes, fats and oil, vegetables, fruits, meat, dairy, coffee, tea, legumes, nuts, sugary foods, mutual adjustment for other beverages (SSB, FJ or LNCB), and energy intake.
Abbreviation: CI, confidence interval; FJ, fruit juices; IPR, incidence proportion ratio; LNCB, low/no-calorie sweetened beverages; MetS, metabolic syndrome; SSB, sugar-sweetened beverages.

[a] imputed with multiple imputation methods.

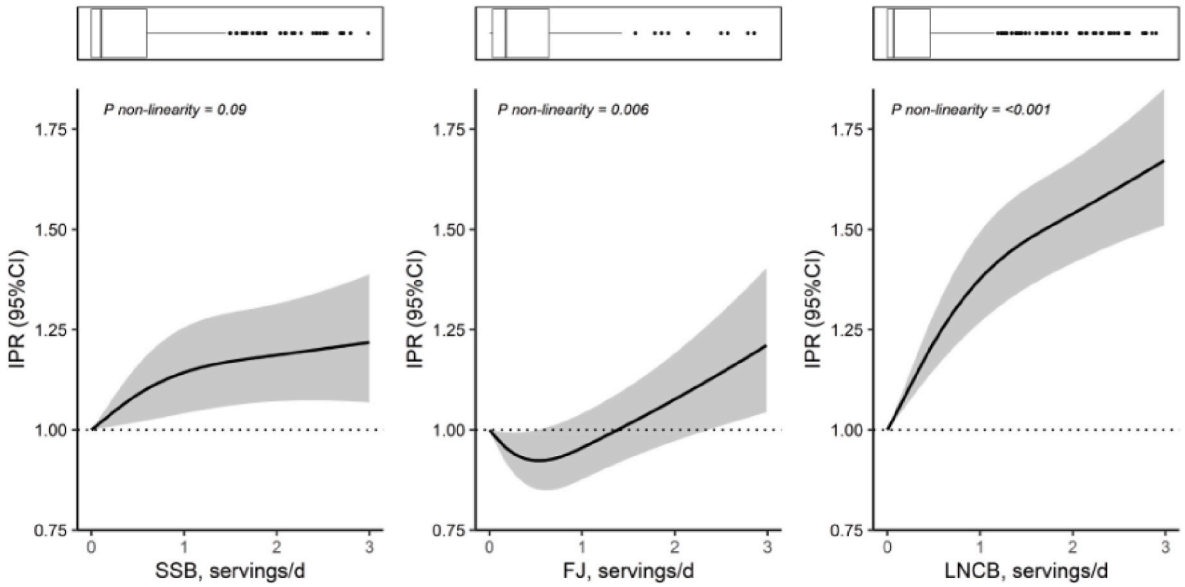

Fig. 1. Dose-response association between servings/day of SSB, FJ, and LNCB intakes and the incidence proportion ratio of MetS in participants of Lifelines. The solid line is the risk estimates evaluated using restricted cubic splines indicating the shape of the associations, whereas the grey areas indicate 95 % confidence intervals. Three knots with 0 g/day as a reference value was placed and model was adjusted for age, sex, education background, moderate physical activity, sedentary behaviour, smoking status, alcohol intake, grains, potatoes, vegetables, fruits, meat, dairy, coffee, tea, legumes, nuts, fats and oils, sugary foods, mutual adjustment for other beverages (SSB, FJ, or LNCB), and energy intake.

lifestyle factors (IPR $_{0-<2\ \text{servings/week}}$ 0.90, 95%CI 0.83–0.97 and IPR $_{2-<7\ \text{servings/week}}$ 0.86, 95%CI 0.79–0.94) (Table 3). After further adjustment for other dietary factors, the inverse association remained for the intake level of 2-<7 servings/week (IPR 0.89, 95%CI 0.82–0.96). The association between FJ and MetS was modified by sex ($p = 0.01$) and BMI ($p = 0.02$). Stratified analyses revealed that the statistically significant inverse associations for intake level of 2-<7 servings/week only remained among women (IPR 0.86, 95%CI 0.77–0.97) and those with BMI<25 kg/m^2 (IPR 0.78, 95%CI 0.63–0.97) (Supplemental Table 3). At higher intake levels, an adverse association was observed among men (IPR 1.16, 95%CI 1.00–1.36), but not among women (IPR 0.95, 95%CI 0.79–1.13). In Lifelines, additional adjustment for BMI did not substantially change the main findings, while exclusion of those who had the desire to lose weight showed that significant association was observed among those with BMI<25 (IPR 1.14, 95%CI 1.00–1.31) but not among those with higher BMI (IPR 1.02, 95%CI 0.90–1.17) (Supplemental Table 4). Replacing SSB with FJ did not yield evidence of an association with MetS incidence (IPR 0.99, 95%CI 0.93–1.06) (Table 4).

Dose-response analysis in Lifelines showed evidence of a non-linear association of LNCB and MetS incidence after adjustment for demographic, lifestyle factors, and other dietary intake factors (*p non-linearity* = <0.001) (Fig. 1). However, analysis by intake categories in Lifelines did not indicate a clear trend of non-linearity, with risk estimates increasing with higher intakes (IPR $_{>0-2\ \text{servings/week}}$ 1.07, 95%CI 0.99–1.17, IPR $_{2-<7\ \text{servings/week}}$ 1.22, 95%CI 1.13–1.32, and IPR $_{\geq 7\ \text{servings/week}}$ 1.57, 95%CI 1.43–1.71; *p linear trend* = <0.001) (Table 3). Pooled analyses of three cohorts showed an adverse association between each serving of LNCB and MetS incidence after adjustment for age and sex (IPR 1.38, 95%CI 1.01–1.76), which became non-significant after further adjustment for demographic, lifestyle and other dietary factors (IPR 1.59, 95%CI 0.74–2.43) (Table 2). High heterogeneity was observed for this association (I^2 94 %, $p < 0.01$). When looking into the individual studies, adverse associations were observed in Lifelines (IPR 1.17, 95%CI 1.14–1.21) and Feel4Diabetes (IPR 2.48, 95%CI 1.60–3.86) while no significant association was observed in NQplus (IPR 1.16, 95% CI 0.78–1.74). Adjustment by BMI further attenuated the associations in all cohorts (Supplemental Table 4). In Lifelines, additional analyses on each MetS parameter confirmed the main finding (Supplemental Table 5). When excluding those who had a desire to lose weight in Lifelines, a stronger adverse association was observed in people with a BMI<25 kg/m^2 (IPR 1.15, 95%CI 1.02–1.30). Additional analyses in Lifelines did not show any interaction with sex or BMI categories (Supplemental Table 3). Theoretical substitution analyses revealed an adverse association with MetS risk when SSB was replaced with LNCB (IPR 1.11, 95%CI 1.06–1.16), which attenuated after additional adjustment for BMI (IPR 0.99, 95%CI 0.94–1.04) (Supplemental Table 4).

4. Discussion

In this prospective study, pooled analyses showed that each additional serving/day of SSB was associated with a 6 % higher risk of MetS incidence. A potential J-shaped association was observed between FJ and MetS risk as displayed by an inverse association at intake levels of 2-<7 servings/week and no associations at lower or higher intake levels. Based on the pooled results, LNCB intake or replacing SSB with LNCB were not significantly associated with MetS risks, but findings across studies were inconsistent indicating adverse associations in Lifelines and Feel4Diabetes and no association in NQplus.

Our findings on the adverse association between SSB and MetS incidence are in line with previous meta-analyses [18,19,39–41]. To illustrate, a meta-analysis of six prospective cohort studies showed an adverse linear association with a 14 % higher incidence of MetS for each 335 ml/day increment of SSB intake (95%CI 1.05–1.23) [39]. Similar findings were observed in a meta-analysis of 15 studies (nine cross-sectional, one case-control, and five prospective studies), which showed a 19 % higher MetS risk for each additional 250 ml/day of SSB [19]. Effect estimates in our study were relatively small as compared to the pooled risk estimate of this meta-analysis, though comparable to the results of included prospective studies. Adverse associations between SSB and disease risks including MetS may be explained by several biological mechanisms, including inducing *de novo* lipogenesis due to high fructose content and incomplete compensation after liquid calorie intake, which contributes to weight gain [14].

We observed a J-shaped association between moderate FJ intake and

Table 3
Adjusted associations between SSB, FJ, and LNCB intakes and MetS incidence for categories of intake in participants of Lifelines.

	IPR (95%CI)				*p*-trend
	No intake	0-<2 servings/ week	2-<7 servings/ week	≥7 servings/ week	
SSB					
N total/ N(%) cases	21306/ 1479 (6.9)	15660/870 (5.6)	12651/864 (6.8)	8603/640 (7.4)	
Model 1	1 (ref)	0.82 (0.75–0.89)	1.06 (0.97–1.15)	1.22 (1.11–1.34)	<0.001
Model 2	1 (ref)	0.84 (0.77–0.91)	1.04 (0.95–1.13)	1.10 (1.00–1.22)	<0.001
Model 3	1 (ref)	0.94 (0.86–1.02)	1.07 (0.98–1.17)	1.13 (1.02–1.26)	0.002
FJ					
N total/ N(%) cases	12832/ 1004 (7.8)	19576/1222 (6.2)	19719/1185 (6.0)	6093/442 (7.3)	
Model 1	1 (ref)	0.83 (0.76–0.90)	0.79 (0.73–0.86)	1.00 (0.90–1.12)	0.5
Model 2	1 (ref)	0.90 (0.83–0.97)	0.86 (0.79–0.94)	1.06 (0.95–1.18)	0.26
Model 3	1 (ref)	0.93 (0.86–1.01)	0.89 (0.82–0.96)	1.06 (0.94–1.18)	0.34
LNCB					
N total/ N(%) cases	25588/ 1557 (6.1)	12679/751 (5.9)	12519/865 (6.9)	7434/680 (9.1)	
Model 1	1 (ref)	0.99 (0.91–1.08)	1.22 (1.13–1.32)	1.68 (1.54–1.83)	<0.001
Model 2	1 (ref)	1.04 (0.96–1.13)	1.23 (1.14–1.33)	1.62 (1.49–1.77)	<0.001
Model 3	1 (ref)	1.07 (0.99–1.17)	1.22 (1.12–1.32)	1.57 (1.43–1.71)	<0.001

Model 1: adjusted for age and sex.
Model 2: model 1 + education background, moderate physical activity, sedentary behaviour, smoking status, alcohol intake.
Model 3: model 2 + grains, potatoes, fats and oil, vegetable, fruit, meat, dairy, coffee, tea, legumes, nuts, sugary foods, mutual adjustment for other beverages (SSB, FJ or LNCB) + energy intake.
Abbreviation: CI, confidence interval; FJ, fruit juices; IPR, incidence proportion ratio; LNCB, low/no-calorie sweetened beverages; MetS, metabolic syndrome; SSB, sugar-sweetened beverages.

Table 4
Adjusted associations of between substitution of SSB with FJ or LNCB with MetS for each serving (150 ml) per day increment in participants of all cohorts.

	IPR (95%CI)			Pooled	
	Lifelines	NQPlus[a]	Feel4Diabetes[a]	IPR (95%CI)	I^2, *p value*
N total/ N(%) cases	58220/ 3853 (6.6)	1094/47 (4.3)	342/39 (11.4)		
SSB by LNCB					
Model 1	1.09 (1.04–1.13)	1.42 (0.53–3.81)	1.51 (0.85–2.67)	**1.20 (0.90–1.51)**	19 %, 0.29
Model 2	1.11 (1.07–1.16)	1.47 (0.55–3.98)	1.69 (0.97–2.96)	**1.33 (0.90–1.75)**	57 %, 0.10
Model 3	1.11 (1.06–1.16)	1.57 (0.54–4.43)	1.98 (1.15–3.39)	**1.49 (0.89–2.10)**	81 %, <0.01
Model 4	1.11 (1.06–1.16)	1.56 (0.55–4.45)	NA		
SSB by FJ					
Model 1	0.91 (0.85–0.98)	1.18 (0.44–3.15)	0.57 (0.21–1.57)	**0.91 (0.84–0.98)**	0 %, 0.69
Model 2	0.97 (0.91–1.04)	1.30 (0.48–3.98)	0.57 (0.20–1.68)	**0.97 (0.90–1.04)**	0 %, 0.63
Model 3	0.99 (0.93–1.06)	1.44 (0.52–4.00)	0.43 (0.12–1.51)	**0.99 (0.93–1.06)**	0 %, 0.47
Model 4	0.99 (0.93–1.06)	1.44 (0.55–3.99)	NA		

Model 1: adjusted for age and sex.
Model 2: model 1 + education background, moderate physical activity, sedentary behaviour, smoking status, alcohol intake.
Model 3: model 2 + grains, potatoes, fats and oil, vegetables, fruits, meat, dairy, coffee, tea, legumes, nuts, sugary foods.
Model 4: model 3 + energy intake.
Abbreviation: CI, confidence interval; FJ, fruit juices; IPR, incidence proportion ratio; LNCB, low/no-calorie sweetened beverages; MetS, metabolic syndrome; SSB, sugar-sweetened beverages.
[a] imputed with multiple imputation methods.

MetS incidence, which is in agreement with previous studies [39,42–44]. For example, a meta-analysis by Semnani-Azad et al. (2020) including three cohorts on mixed FJ and two cohorts on 100%FJ showed an inverse association between moderate intake of each type of FJ (125 ml/day) and MetS incidences with RRs of 0.58 (95%CI 0.42–0.79) and 0.77 (95%CI 0.61–0.97) [39]. Although underlying pathways explaining associations between FJ and disease outcomes required further investigation, one of the answers may relate to the fact that in addition to sugar, FJ also contains vitamins, minerals, fibres and polyphenols [42,43]. It may be postulated that these nutritive compounds explain the inverse association at lower FJ intake levels whereas the impact of sugar may overrule that inverse association at higher intake levels.

Our pooled analyses indicate no significant association between LNCB intake - or replacement of SSB by LNCB - with MetS risks. Evidence from observational studies generally showed adverse associations between LNCB and metabolic outcomes [18–20,45]. A meta-analysis of three prospective cohort studies showed a 32 % higher MetS risk (95%CI 1.21–1.44) when comparing the highest vs lowest LNCB intake group [18]. Another meta-analysis including four studies (two cross-sectional and two prospective studies) also showed a 31 % higher MetS risk for each 250 ml/day increment of LNCB intake (95%CI 1.05–1.65) [19]. To our knowledge, replacing SSB with LNCB in association with MetS incidence specifically - as performed in our study - has not been done before. However, a recent meta-analysis of three cohorts substituting SSB with LNCB reported lower body weight (three cohorts; MD -0.12 kg/y, 95%CI -0.14, −0.10) [46]. Conversely, our previous meta-analyses using four European studies, including Lifelines, showed no association between replacing SSB with LNCB -or water- and weight and waist circumference change [20]. Yet, it should be noted that despite efforts to harmonize datasets and standardize covariate adjustments, notable inconsistencies were observed across studies. We observed adverse associations in Lifelines and Feel4Diabetes, which attenuated after additional adjustment for baseline BMI. This attenuation may be attributed to the strong correlation between BMI and waist circumference, a key parameter in metabolic syndrome, as also observed in a study by Nettleton et al. (2009) [47]. However, as we did not observe this attenuation for SSB and FJ, it may also be speculated that BMI acts as an intermediate in the association between LNCB and MetS specifically. Finally, the observed association may also be the result of reverse causality, i.e., participants with higher waist circumference and overweight/obesity may use more LNCB to limit sugar intake, which may in turn explain the substantially stronger adverse association observed in Feel4Diabetes than in Lifelines and NQPlus. The biological explanation for the association between LNCB and MetS, if present, remains unclear. The most prevailing hypothesis suggests that low/no-caloric sweeteners may induce gut microbiota dysbiosis, leading to insulin resistance and metabolic disease development [48,49]. However, this preliminary observation warrants further investigation, particularly in human studies, to confirm or refute this hypothesis [45,50].

An important strength of this study includes the use of harmonized data from several European population-based studies, with the possibility to control for a wide range of relevant confounders. In addition, the large sample size of Lifelines allowed us to conduct well-powered stratified analyses. A limitation is the use of self-reported FFQs, which

were not specifically designed for assessing sweetened beverages or sweeteners intake, preventing the distinction between various products and sweeteners with potentially different metabolic effects [45]. We were also unable to differentiate between types of juice i.e., freshly squeezed vs commercial which may have varying nutrient content, especially fibre, due to industrial processing. Additionally, we were unable to distinguish between 100 % juice and those with added sugar, which may have distinct impact on health given the sugar level. Furthermore, dietary intake was estimated solely at baseline. Repeated assessment could have resulted in more precise and robust risk estimates and reduced the possibility of reverse causality [46]. Moreover, data on medication use at follow-up was not available in Lifelines, which may have resulted in misclassification of those having MetS but not being classified as such. Finally, while we adjusted for numerous confounders, residual confounders may still have occurred. However, sensitivity analyses in Lifelines using the E-value indicate that this is unlikely (data not shown). To nullify the association, any unmeasured confounder should be strongly associated with both exposure and outcome, which we consider unlikely given the wide range of confounders already considered.

To conclude, this study showed an association between SSB intake and a higher risk of MetS incidence. A J-shaped association was observed between moderate intake of FJ and MetS when compared to no intake. Our findings for LNCB revealed a notable degree of inconsistency across studies, making it difficult to determine if LNCB can be a beneficial alternative to SSB. Therefore, further study on this topic with longer follow-up, repeated dietary intake, and more detailed dietary data and biomarkers, is required.

Author contribution

JAH, JCGH, and AR are coordinators of the SWEET EU project and together with EJMF initiated the research question. NDN analysed the data. NDN and EMB-B interpreted the results and drafted the manuscript. NDN, EMB-B, MECB, SSS-M, CM, JMG, YM and EJMF discussed the results and reviewed the draft manuscript. All authors critically revised the manuscript and approved the final version of the manuscripts.

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Data statement

Data that support the findings of this study are available from each cohort centre but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available upon reasonable request pending application, payment (if required from each cohort centre), and SWEET consortium agreement.

Declaration of competing interest

SSM-M has received recent research funding for epidemiological studies on dairy products and cardiometabolic diseases from the Dutch Dairy Association and the Danish Dairy Research Foundation. JCGH is a member of Dupont/IFF and Mars Scientific Advisory Boards and has received honorariums from the International Sweeteners Association together with AR. JCGH and JAH are also conducting the SWITCH trial funded by the American Beverage Association. JCGH and AR have received an honorarium from Unilever, the International Sweeteners Association, and Nestlé. In the past, EJMF has received an unrestricted grant from Friesland Campina and the European Beer Institute and conducted a study on added sugar and individual sugars partly funded by Kenniscentrum Suiker en Gezondheid (2011). Other authors have no conflicts of interest to be disclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.09.014.

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