General Psychiatry

Consumption of sugary beverages, genetic predisposition and the risk of depression: a prospective cohort study

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To cite: Chen Y, Yang H, Sheng B, *et al*. Consumption of sugary beverages, genetic predisposition and the risk of depression: a prospective cohort study. *General Psychiatry* 2024;**37**:e101446. doi:10.1136/gpsych-2023-101446

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gpsych-2023-101446).

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Received 20 November 2023
Accepted 07 June 2024

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ABSTRACT

Background The associations between sugary beverages and genetic predisposition to depression risk remain unclear.

Aims This study aimed to investigate the associations of sugar-sweetened beverages (SSBs), artificially sweetened beverages (ASBs) and natural juices (NJs) with depression and to assess whether these associations were modified by genetic predisposition.

Methods We used data from the UK Biobank of 180 599 individuals aged 39–72 years who were depression-free at baseline. Dietary intake of SSBs, ASBs and NJs was accessed by a 24-hour dietary recall between 2009 and 2012. The Polygenic Risk Score for depression was estimated and categorised as low (lowest tertile), intermediate (tertile 2) and high (highest tertile). Cox proportional hazard and substitution models were conducted to evaluate hazard ratios (HRs) and 95% CIs.

Results Over the 12-year follow-up, 4915 individuals developed depression. Higher consumption (>2 units/day) of SSBs (HR: 1.26, 95% CI 1.12 to 1.43) and ASBs (HR: 1.40, 95% CI 1.23 to 1.60) were both associated with an increased risk of depression. However, moderate consumption (>0–1 units/day) of NJs was associated with a lower risk of depression (HR: 0.89, 95% CI 0.83 to 0.95). Furthermore, genetic predisposition did not modify these associations (p interaction>0.05). In substitution models, the HRs for depression risk were 0.94 (95% CI 0.89 to 0.99) and 0.89 (95% CI 0.85 to 0.94), respectively, when 1 unit/day of SSBs or ASBs was replaced by an equivalent intake of NJs.

Conclusions Higher consumption of SSBs and ASBs was associated with an increased risk of depression; in contrast, moderate consumption of NJs was inversely associated with a lower risk of depression. In theory, substituting SSBs and ASBs with NJs would suppose a reduction of depression risk.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Higher consumption of sugar-sweetened beverages (SSBs) is linked with a higher risk of depression, although several studies showed inconsistent findings.
⇒ Artificially sweetened beverages (ASBs) and natural juices (NJs) are used as 'healthy' substitutes to reduce the consumption of SSBs.
⇒ Few studies have examined associations between these beverages and depression and whether these associations were modified by genetic predisposition in large cohort studies.

WHAT THIS STUDY ADDS

⇒ We found that higher consumption of SSBs and ASBs was associated with a higher risk of depression. In contrast, moderate consumption of NJs was associated with a lower risk of depression. These associations were not significantly modified by genetic predisposition to depression.
⇒ We also observed that substituting SSBs and ASBs with equivalent consumption of NJs could be associated with a risk reduction of depression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results suggest that shifting toward NJs as a healthy alternative to SSBs and ASBs may help to prevent depression.

INTRODUCTION

Depression is one of the most common mental health disorders and has been a major public health concern. Estimates from the Global Burden of Disease Study 2019 report that depression is a leading cause of global disease burden, affecting more than 300 million people worldwide.[1] Suicide can be partially attributed to depression, as available evidence suggests that up to 15% of those with mood disorders commit suicide, and approximately 50% of those who attempt suicide suffer from depression.[2] Although antidepressant maintenance therapy is the mainstay in the management of depression, problems such as the lack of therapeutic efficacy, a high relapse rate and insufficient treatment expenditure from individuals persist, severely affecting the quality of life and survival of patients with depression. Given the increasing incidence of depression, there is growing interest in identifying modifiable lifestyle factors to prevent the disorder.

The consumption of sugar-sweetened beverages (SSBs), including soft drinks, cordials and sports drinks, has rapidly increased worldwide

in recent decades. It is estimated that SSBs are responsible for an average of up to 180 000 deaths per year due to obesity, obesity-related cancers, diabetes and cardiovascular disease.[3] Accumulating evidence from epidemiological studies has demonstrated adverse associations of SSBs with hypertension,[4] diabetes[5] and cardiovascular disease.[6] Yet, the few cross-sectional studies that have examined the association between SSBs and depression show inconsistent results.[7 8] Data from the National Institutes of Health–American Association of Retired Persons Diet and Health Study showed that frequent consumption of SSBs was associated with an approximately 1.30-fold increased risk of depression.[7] However, another cross-sectional study conducted in the Whitehall Study II found no association between SSBs and the risk of depression.[8] Currently, several beverages are recognised as 'healthy' alternatives with low-calorie content, such as artificially sweetened beverages (ASBs) and natural juices (NJs), which are popular approaches to reducing SSBs consumption. However, the association between ASBs and NJs consumption with the risk of chronic diseases remains controversial.[9–12] For example, several studies have found that ASBs and NJs were associated with increased risks of weight gain, type 2 diabetes and mortality,[9 10] whereas other studies reported their beneficial effects for type 2 diabetes, hypertension and mortality.[11 12] The substitution analysis method can assess the impact of substituting one type of beverage with another on health outcomes, assuming that total daily energy intake remains constant.[13] To our knowledge, no study has examined the longitudinal association of ASBs and NJs with depression.

Depression is a complex disease driven by both environmental factors and genetic predisposition, with a heritability of 37%.[14] To date, several genome-wide association studies (GWAS) have identified some single-nucleotide polymorphisms (SNPs) associated with the development of depression.[15] Polygenic risk scores (PRSs), which aggregate the cumulative effect of many genetic variants, have commonly emerged as a quantitative measure to identify the total genetic effect contributing to depression risk effectively. Indeed, genetic susceptibility may interact with environmental factors to modify disease risk. However, it remains largely unclear whether genetic predisposition modifies the association of three types of beverages with depression risk.

Therefore, using a large population-based cohort from the UK Biobank, we aimed to examine the associations of SSBs, ASBs and NJs with the incidence of depression and to assess whether these associations are modified by genetic predisposition. In addition, we used the substitution analysis method to investigate the substitution effect of theoretically equivalent intakes of SSBs and ASBs with NJs.

METHODS

Study design and population

The UK Biobank is an ongoing prospective cohort study initiated between April 2006 and December 2010 at 22 recruitment centres in Wales, England and Scotland. Over 0.5 million participants aged 37–73 years have provided demographic characteristics, lifestyle factors and health information through touch-screen questionnaires, computer-assisted interviews and physical and functional measures.[16] In the current analyses, we excluded 29 610 participants with prevalent depression (based on information from self-report, hospital admissions and death records), 273 831 participants who did not participate in the 24-hour recall questionnaire, 15 615 participants of non-white British ancestry or without genetic data and 2852 participants with extreme mean energy intakes (men with <800 kcal/day or >4200 kcal/day or women with <600 kcal/day or >3500 kcal/day), leaving 180 599 participants for the present study (see figure 1).

Dietary assessment

Dietary information was collected five times between 2009 and 2012 using a web-based 24-hour dietary recall questionnaire. In this validated questionnaire, participants were asked how many units (glasses/cartons/250 mL/cans) of SSBs (fizzy and squash drinks), ASBs (low-calorie and diet drinks) and NJs (pure orange juice, pure grapefruit juice and other NJs) they had consumed in the previous 24 hours. They selected either the following intake amounts: none, 0.5, 1, 2, 3, 4, 5 and 6+ for each of the above beverages. One unit was equal to approximately 250–330 mL. Of the 180 599 individuals included in this study, 69 462 (38.5%) completed the questionnaire once, 41 655 (23.1%) two times, 37 282 (20.6%) three times, 27 049 (15.0%) four times and 5151 (2.9%) five times. In the present analyses, we used the mean dietary intake for participants who answered the questionnaire at least once.

Assessment of PRS

A PRS for depression provides a quantitative estimate of genetic predisposition, which is calculated from the cumulative effect of multiple genetic variants. The score was computed according to the meta-analysis of summary statistics from the GWAS for depression in the Genetic Epidemiology Research on Adult Health and Aging.[17] As the sample was predominantly of European ancestry, our analyses were restricted to individuals from European samples in the UK Biobank. Polygenic risk score-continuous shrinkage (PRS-CS) was applied to infer posterior effect sizes of SNPs on depression, using a Bayesian regression framework to place continuous shrinkage priors on SNP effect sizes. PRS-CS uses linkage disequilibrium (LD) information from an external reference panel to model local LD patterns and update effect sizes jointly for all the SNPs in LD. Thus, it contains various genetic architectures and eliminates determination regarding pruning and the selection of GWAS threshold. Based on GWAS summary statistics of 61 847 cases (7892 cases and 53 955 controls) for major depressive disorder, the weights were derived using the PRS-CS method with default parameters and 1000 Genomes European as the LD reference panel. In the UK Biobank dataset, a total of 1 065 182 autosomal SNPs were retained. An individual-level polygenic score was then calculated by multiplying the number of risk alleles of each SNP weighted by the corresponding posterior effect sizes across all SNPs (n=1 065 182) in the UK Biobank,

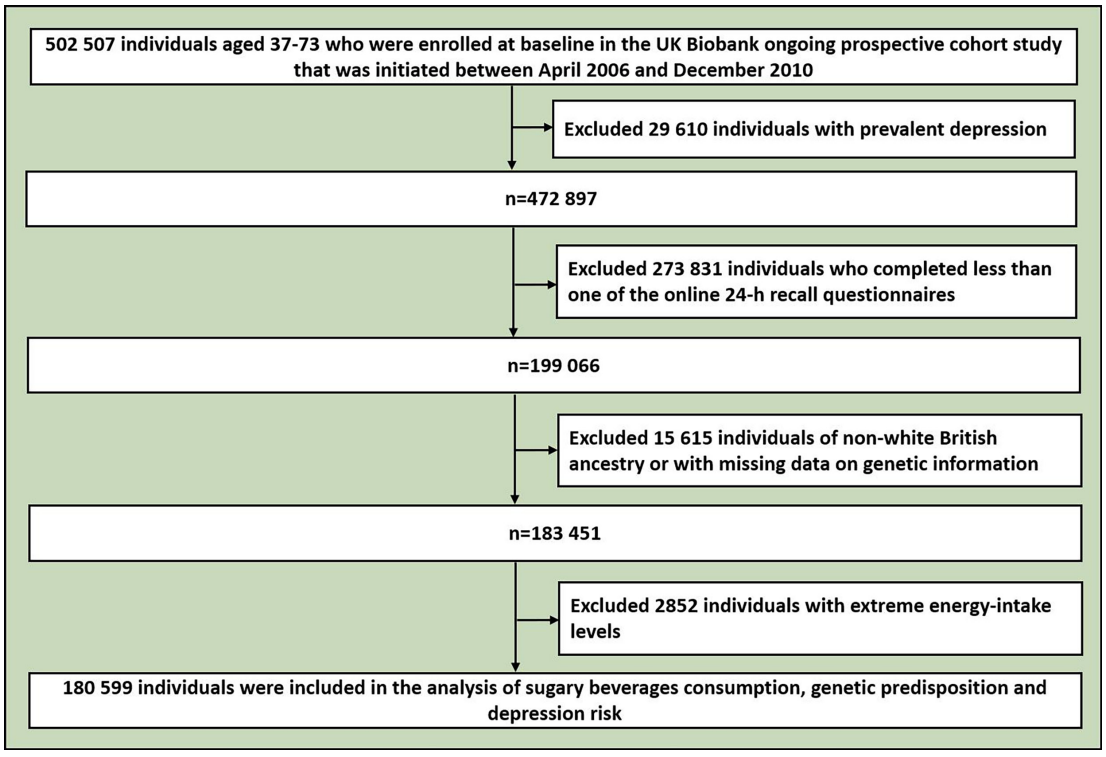

Figure 1 Flowchart for the selection of the analysed study sample from the UK Biobank Study.

which was performed using the '-score' command in PLINK. According to the Z-standardised PRS in the total population, participants were divided into three groups: low (lowest tertile), middle (tertile 2) and high (highest tertile).

Ascertainment of depression

Incident depression in the UK Biobank was defined if participants had either hospital admissions data (hospital primary/secondary diagnosis) or national death registry records (death primary and contributory). The information on hospital admissions and death records (from the Hospital Episode Statistics for England, the Scottish Morbidity Record data for Scotland and the Patient Episode Database for Wales) were determined by the International Classification of Diseases (ICD-10)[18] codes (ICD-10: F32-F34, F38 and F39).

Assessment of covariates

Information on sociodemographic characteristics (sex, age, educational level and socioeconomic status) and lifestyle factors (physical activity, smoking status, alcohol intake frequency and diet pattern) was obtained through self-reported questionnaires. Educational level was classified into college or university degree, upper secondary, lower secondary, vocational and others. Socioeconomic status was determined using the Townsend Deprivation Index, a composite score based on four key factors, including unemployment, household overcrowding, non-car ownership and non-home ownership; it was classified as low (highest quintile), middle (quintiles 2–4) and high (lowest quintile). Physical activity was defined using the Metabolic Equivalent Task (MET) Score and categorised as low (<600 MET-min/week), moderate (600–3000 MET-min/week) and high (>3000 MET-min/week) according to the International Physical Activity Questionnaire. Smoking status was classified as never, previous and current smokers. The frequency of alcohol drinking was classified as never, special occasions only, one to three times a month, once or two times a week, three or four times a week and daily or almost daily. A healthy diet pattern was derived from the Food Frequency Questionnaire and was composed of at least four of the following seven categories: fruits, ≥3 servings/day; vegetables, ≥3 servings/day; fish, ≥2 servings/week; processed meats, ≤1 serving/week; unprocessed red meats, ≤1.5 servings/week; whole grains, ≥3 servings/day; and refined grains, ≤1.5 servings/day (see online supplemental table1). Total energy intake (kcal/day) was assessed using the 24-hour dietary questionnaire. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square metres. Comorbidities (hypertension and diabetes) were determined from touchscreen questionnaires, medical examinations and hospital inpatient records.

Statistical analysis

Baseline characteristics were determined between incident depression presented as percentages for categorical variables, means with SDs for normal continuous variables and medians and interquartile ranges (IQRs) for non-normal variables. Statistical differences in each characteristic between the two categories were compared using χ^2 tests, t-tests and Mann-Whitney U tests, respectively.

Cox proportional hazard models were used to estimate the hazards (HRs) and 95% CIs of incident depression for the consumption of SSBs, ASBs and NJs. Follow-up time was

calculated from the date of the 24-hour dietary questionnaire completion to the diagnosis of depression, loss to follow-up, death or the end of the study period (30 September 2021), whichever came first. The proportional hazards assumption was assessed using Schoenfeld residuals, and the proportional hazards assumption was upheld. The Cox regression model was adjusted for sex, age, socioeconomic status and education level in model 1. Model 2 was further adjusted for BMI, smoking status, alcohol intake frequency, physical activity, diet pattern, total energy intake, hypertension and diabetes. SSBs, ASBs and NJs were adjusted for each other. Model 3 was additionally adjusted for covariates in model 2 plus genetic predisposition. P values for trend were calculated by treating categorical exposure variables as continuous in Cox proportional hazard models. Missing values of covariates were imputed using multiple imputations based on five replications using chained equations. We further investigated the dose–response associations between SSBs, ASBs and NJs and depression risk using restricted cubic spline regressions with four knots at the 25th, 50th, 75th and 95th centiles. In addition, we assessed the joint effect of SSBs, ASBs and NJs with genetic predisposition on the risk of new-onset depression. Participants were divided into 12 groups according to genetic predisposition and specific beverage categories, with low PRS and non-consumers as the reference group. A cross-product term was included in models to test for interactions between beverages and genetic predisposition, and its coefficient was tested using the Wald test.

In addition, the substitution analyses were used to estimate the theoretical result of substituting SSBs and ASBs with NJs for the same amount of consumption on the risk of depression, assuming that total energy intake is known and constant.[13] The difference in their β coefficients of the two beverages being compared, along with the variances and covariances were used to estimate the HRs and 95% CIs for the substitution. The intake of each food or nutrient is interdependent. To some extent, the substitution model addresses the limitation of analysing the effects of individual foods or nutrients.

Furthermore, several sensitivity analyses were conducted to examine the robustness of our findings: (1) to minimise the influence of reverse causation, we excluded participants who developed depression during the first 3-year follow-up (n=177 934); (2) we tested associations between absolute quantity (mL/day) of SSBs, ASBs and NJs and the risk of depression (n=180 699); (3) to represent long-term usual beverage consumption habits, only participants who took part in at least two dietary assessments were included in the analyses (n=111 237); (4) to investigate the effect of different diet pattern (Alternate Mediterranean Diet Score (AMED)) on these associations, we adjusted for AMED diet pattern as a covariate (n=180 699); (5) to ensure the 24-hour dietary intake was typical, participants with untypical 24-hour diet were excluded (n=180 587); (6) to assess the potential confounding factor of diabetes, we repeated the main analyses by excluding participants with diabetes and abnormal glucose tolerance (random blood glucose≥11.1 mmol/L, or glycated haemoglobin≥6.5 % or had been diagnosed by self-report, primary care data or hospital admissions at baseline) (n=172 546); (7) to evaluate the stability of the results under multiple imputation methods, analyses were repeated by excluding participants with missing covariates (n=93 669); and (8) competing risk regression models by the method of Fine and Gray were used to account for the competing risk of death (n=180 699).

All statistical analyses were performed using STATA V.15 statistical software (StataCorp) and R Statistical Software (V.4.2.1). The two-sided p<0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Overall, 180 599 participants (median (IQR) age: 58 (50–63); 45.8% men) were included in the current study. NJs had the highest relative contribution to the total amount of sugary beverage consumption at 43%, followed by SSBs and ASBs at 33% and 24%, respectively (see online supplemental figure 1). Table 1 displays the baseline characteristics of eligible participants according to incident depression. Compared with characteristics of participants who did not develop depression, those who developed depression were more likely to be female, obese, smokers and have a lower education level, lower socioeconomic status, higher frequency of alcohol intake, healthy diet, higher energy intake, higher prevalence of hypertension and diabetes and a higher PRS. Baseline characteristics of the study population by the consumption of SSBs, ASBs and NJs are also presented in the online supplemental table 2. The proportion of >2 units/day of SSBs, >2 units/day of ASBs and >0–1 units/day of NJs were 4.3% (n=7777), 3.1% (n=5562) and 38.1% (n=68 871), respectively. During 1 749 954 person-years of follow-up (median: 9.5 years, IQR: 9.4–10.2 years), 4915 depression cases were recorded.

Association of SSBs, ASBs and NJs with incident depression

In online supplemental figure 2, the dose–response relationship of SSBs and NJs with depression showed U-shaped associations (SSBs: χ^2 value=4.14, p for non-linear=0.042; NJs: χ^2 value=29.80, p for non-linear<0.001). However, there was no non-linear relationship between ASBs and depression (χ^2 value=1.98, p for non-linear=0.160).

In basic-adjusted and multi-adjusted Cox models, SSBs, ASBs and NJs were associated with the risk of depression (see table 2). Specifically, a total multivariable adjustment showed that >2 units/day of SSBs was associated with a 1.26-fold higher risk of depression (HR: 1.26, 95% CI 1.12 to 1.43) compared with non-drinkers (p for trend=0.001). Higher consumption of ASBs was also related to an increased risk of depression (p for trend<0.001), with consumption of >1–2 units/day associated with a 1.16-fold hazard (HR: 1.16, 95% CI 1.03 to 1.30) and the HR for consumption of >2 units/day was 1.40 (95% CI 1.23 to 1.60). However, participants who reported consuming >0–1 unit/day (HR: 0.89, 95% CI 0.83 to 0.95) or >1–2 units/day (HR: 0.89, 95% CI 0.80 to 0.98) of NJs were at decreased risk of depression (p

Table 1 Baseline characteristics of the study participants according to incident depression

Characteristic	n (%)	Incident depression		F/Z/χ^2 value*	P value
		No	Yes		
Total (n)	180599	175684	4915		
Age, mean (IQR), year	58 (50–63)	58 (50–63)	58 (50–63)	2.04	0.064
Male	82760 (45.8)	80953 (46.1)	1807 (36.8)	1.00×10^3	<0.001
Education level				1.60×10^3	<0.001
College/university degree	76608 (42.4)	74948 (42.7)	1660 (33.8)		
Upper secondary	23814 (13.2)	23204 (13.2)	610 (12.4)		
Lower secondary	45545 (25.2)	44090 (25.1)	1455 (29.6)		
Vocational	9953 (5.5)	9637 (5.5)	316 (6.4)		
Others	24679 (13.7)	23805 (13.5)	874 (17.8)		
Socioeconomic status†				2.30×10^3	<0.001
1 (least deprived)	40421 (22.4)	39517 (22.5)	904 (18.4)		
2–4	113254 (62.7)	110298 (62.8)	2956 (60.1)		
5 (most deprived)	26924 (14.9)	25869 (14.7)	1055 (21.5)		
BMI (kg/m^2)				2.00×10^3	<0.001
<25	67186 (37.2)	65733 (37.4)	1453 (29.6)		
25 to <30	76092 (42.1)	74123 (42.2)	1969 (40.1)		
≥30	37321 (20.7)	35828 (20.4)	1493 (30.4)		
Smoking status				2.60×10^3	<0.001
Never	102001 (56.5)	99673 (56.7)	2328 (47.4)		
Previous	65174 (36.1)	63196 (36.0)	1978 (40.2)		
Current	13424 (7.4)	12815 (7.3)	609 (12.4)		
Alcohol intake frequency				3.00×10^3	<0.001
Never	42789 (23.7)	41781 (23.8)	1008 (20.5)		
Special occasions only	47006 (26.0)	46030 (26.2)	976 (19.9)		
One to three times a month	45719 (25.3)	44542 (25.4)	1177 (23.9)		
Once or two times a week	19501 (10.8)	18857 (10.7)	644 (13.1)		
Three or four times a week	16176 (9.0)	15526 (8.8)	650 (13.2)		
Daily or almost daily	9408 (5.2)	8948 (5.1)	460 (9.4)		
Physical activity				589.45	<0.001
Low	32481 (18.0)	31387 (17.9)	1094 (22.3)		
Moderate	95508 (52.9)	93142 (53.0)	2366 (48.1)		
High	52610 (29.1)	51155 (29.1)	1455 (29.6)		
Diet pattern				7.68	0.006
Unhealthy	101564 (56.2)	98895 (56.3)	2669 (54.3)		
Healthy	79035 (43.8)	76789 (43.7)	2246 (45.7)		
Energy, mean (SD), kcal/day	2088.6 (557.2)	2089.6 (556.2)	2053.4 (590.7)	0.66	<0.001
Hypertension				4.00×10^3	<0.001
No	120243 (66.6)	117770 (67.0)	2473 (50.3)		
Yes	60356 (33.4)	57914 (33.0)	2442 (49.7)		
Diabetes				853.45	<0.001
No	172568 (95.6)	168022 (95.6)	4546 (92.5)		
Yes	8031 (4.4)	7662 (4.4)	369 (7.5)		
PRS				87.64	<0.001
Low	61177 (33.9)	59683 (34.0)	1494 (30.4)		
Intermediate	60148 (33.3)	58456 (33.3)	1692 (34.4)		
High	59274 (32.8)	57545 (32.8)	1729 (35.2)		

Continued

Table 1 Continued

Characteristic	n (%)	Incident depression		F/Z/χ^2 value*	P value
		No	Yes		

*Statistical differences in each characteristic between the two categories were compared using χ^2 tests for categorical variables, t-tests for normal continuous variables and Mann-Whitney U tests for non-normal continuous variables.
†Socioeconomic status is assessed using the Townsend Deprivation Index, which combines information on social class, employment, car availability and housing.
BMI, body mass index; IQR, interquartile range; PRS, Polygenic Risk Score.

for trend=0.026). Higher consumption (>2 units/day) of NJs no longer showed a statistically significant association with depression (HR: 1.08, 95% CI 0.92 to 1.27). In addition, each unit/day increase in the consumption of SSBs and ASBs was associated with a 1.05-fold (HR: 1.05, 95% CI 1.02 to 1.09) and 1.10-fold (HR: 1.10, 95% CI 1.07 to 1.14) higher risk of depression.

The joint effect of SSBs, ASBs, NJs and genetic predisposition on depression risk

Compared with participants with low genetic predisposition, the HRs (95% CIs) of depression were 1.15 (1.07 to 1.24) for those with intermediate genetic predisposition and 1.17 (1.09 to 1.26) for those with a high genetic predisposition (see online supplemental table 3). We investigated the joint effect between SSBs, ASBs or NJs with a genetic predisposition to depression (see figure 2). Compared with non-drinkers of SSBs or ASBs with low genetic predisposition, participants with >2 units/day of SSBs and ASBs and high genetic predisposition were at the highest risk of depression (SSBs: HR: 1.61, 95% CI 1.31 to 1.97; ASBs: HR: 1.90, 95% CI 1.54 to 2.34). Conversely, participants with a moderate intake of NJs (>0–1 unit/day) and a low genetic predisposition had the lowest depression risk (HR: 0.86, 95% CI 0.77 to 0.96). In addition, there was no interaction between any of the beverages and genetic predisposition with the risk of depression (SSBs: χ^2 value=0.19, p for interaction=0.667; ASBs: χ^2 value=1.24, p for interaction=0.266; NJs: χ^2 value=0.14, p for interaction=0.710).

The substitution effect of SSBs and ASBs with NJs on the risk of depression

The results of substitution models are shown in figure 3. There were beneficial associations with depression by replacing SSBs and ASBs with an equivalent consumption of NJs. Substituting 1 unit/day of SSBs and ASBs with an equivalent consumption of NJs was associated with a 6% (HR: 0.94, 95% CI 0.89 to 0.99) and 11% (HR: 0.89, 95% CI 0.85 to 0.94) risk reduction of depression, respectively. The HRs (95% CIs) were 0.88 (0.80 to 0.97) and 0.80 (0.73 to 0.88) for substituting 2 units/day of SSBs and ASBs with an equivalent intake of NJs. In addition, replacing 5 units/day of SSBs and ASBs with NJs was substantially associated with 27% (HR: 0.73, 95% CI 0.56 to 0.93) and 43% (HR: 0.57, 95% CI 0.45 to 0.73) lower risk of depression. By contrast, the replacement of SSBs with ASBs was associated with an increased risk of depression (see online supplemental table 4).

Sensitivity analysis

A series of sensitivity analyses were performed to evaluate the robustness of the findings from the main analyses. First, when we excluded the incident depression cases detected in the first 3-year follow-up period, the results were not substantially altered (see online supplemental table 5). Second, when we repeated the main analyses using absolute quantity (mL/day) of SSBs, ASBs and NJs, these associations did not change appreciably (see online supplemental table 6). Third, when restricted to participants with at least two dietary assessments, the magnitude of observed associations remained similar (see online supplemental table 7). Fourth, the associations between sugary beverages and depression were generally unchanged when the AMED diet pattern was adjusted (see online supplemental table 8). Fifth, the results were also consistent with the main analyses when participants with an untypical 24-hour diet were excluded (see online supplemental table 9). Sixth, similar results were observed when the analyses were conducted after excluding participants with diabetes and abnormal glucose tolerance (see online supplemental table 10). Seventh, the results were similar when we conducted analyses by excluding participants with missing covariates (see online supplemental table 11). At last, when considering the competing risk of death, the results were similar to our original analyses (see online supplemental table 12).

DISCUSSION

Main findings

In this large population-based longitudinal study, we found the following: (1) higher consumption (>2 units/day) of SSBs and ASBs was associated with an increased risk of depression; (2) moderate consumption (>0–1 units/day) of NJs was associated with a lower risk of depression; (3) these associations remained regardless of genetic predisposition to depression; and (4) replacing 1 unit/day of SSBs and ASBs with an equivalent consumption of NJs was associated with a significant 6% and 11% reduction in the risk of depression.

Indeed, the association between SSBs consumption and the risk of depression has been controversial. A recent meta-analysis that included ten observational studies demonstrated that higher consumption of SSBs was associated with a 1.31-fold increased risk of depression.[19] Consistently, findings from a cross-sectional survey of 5465 Korean adults revealed that SSBs consumption was positively associated with depression and suicidal ideation.[20] Several lines of evidence, however, indicated that there was no association between SSBs and

Table 2 Multivariable-adjusted HRs for beverage intake categories and depression

	Beverage consumption							
	0 unit/day	>0–1 unit/day	>1–2 units/day	>2 units/day	Per one level increase	P-trend	Per one unit/day increase	P value
Sugar-sweetened beverages								
Incident cases/person-years	3293/1 197 990	944/343 577	398/135 222	280/73 164				
Model 1*	1.00 (Ref.)	1.03 (0.95 to 1.10)	1.13 (1.01 to 1.25)	1.47 (1.30 to 1.66)	1.10 (1.06 to 1.13)	<0.001	1.10 (1.07 to 1.13)	<0.001
Model 2†	1.00 (Ref.)	1.02 (0.95 to 1.10)	1.06 (0.95 to 1.18)	1.27 (1.12 to 1.43)	1.06 (1.02 to 1.09)	0.001	1.05 (1.02 to 1.09)	0.001
Model 3‡	1.00 (Ref.)	1.02 (0.95 to 1.10)	1.06 (0.95 to 1.18)	1.26 (1.12 to 1.43)	1.06 (1.02 to 1.09)	0.001	1.05 (1.02 to 1.09)	0.001
Artificially sweetened beverages								
Incident cases/person-years	3593/1 370 478	717/229 713	347/96 947	258/52 816				
Model 1	1.00 (Ref.)	1.17 (1.08 to 1.27)	1.35 (1.21 to 1.51)	1.82 (1.60 to 2.07)	1.20 (1.16 to 1.24)	<0.001	1.19 (1.15 to 1.22)	<0.001
Model 2	1.00 (Ref.)	1.09 (1.00 to 1.18)	1.16 (1.04 to 1.30)	1.40 (1.23 to 1.60)	1.10 (1.07 to 1.14)	<0.001	1.10 (1.07 to 1.14)	<0.001
Model 3	1.00 (Ref.)	1.08 (1.00 to 1.18)	1.16 (1.03 to 1.30)	1.40 (1.23 to 1.60)	1.10 (1.07 to 1.14)	<0.001	1.10 (1.07 to 1.14)	<0.001
Natural juices								
Incident cases/person-years	2703/847 516	1613/664 064	441/185 085	158/53 289				
Model 1	1.00 (Ref.)	0.82 (0.77 to 0.87)	0.83 (0.75 to 0.92)	1.05 (0.90 to 1.24)	0.92 (0.89 to 0.96)	<0.001	0.96 (0.92 to 1.00)	0.032
Model 2	1.00 (Ref.)	0.89 (0.83 to 0.95)	0.89 (0.80 to 0.98)	1.08 (0.92 to 1.27)	0.96 (0.92 to 0.99)	0.025	0.99 (0.95 to 1.03)	0.522
Model 3	1.00 (Ref.)	0.89 (0.83 to 0.95)	0.89 (0.80 to 0.98)	1.08 (0.92 to 1.27)	0.96 (0.92 to 0.99)	0.026	0.99 (0.95 to 1.03)	0.525

*Model 1 was adjusted for sex, age, socioeconomic status and education level.
†Model 2 was further adjusted for body mass index, smoking status, alcohol intake frequency, physical activity, diet pattern, total energy intake, hypertension and diabetes. Sugar-sweetened, artificially sweetened and natural juices were mutually adjusted.
‡Model 3 was additionally adjusted for the covariates in model 2 plus genetic predisposition.
HRs, hazard ratios; P-trend, p values for trend; Ref., reference.

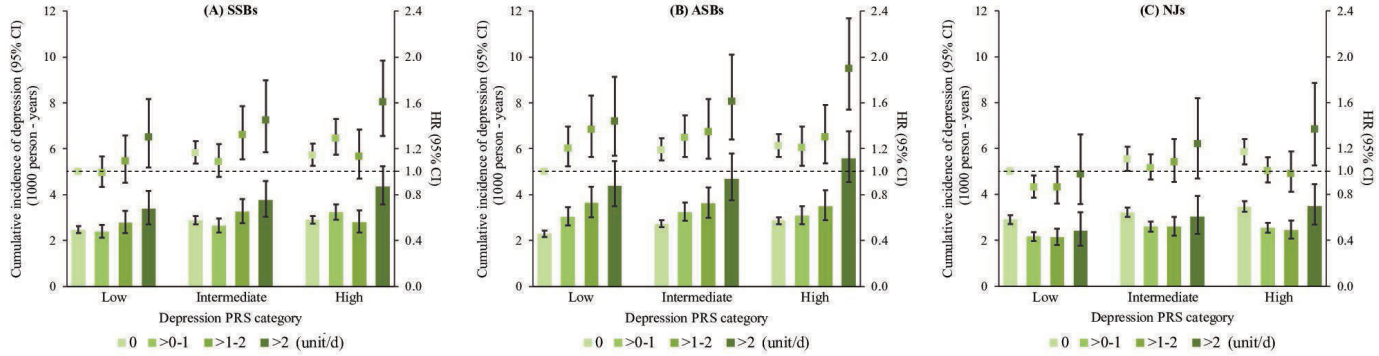

Figure 2 Multivariable-adjusted HRs of the joint effect of beverage intake categories and genetic predisposition on depression, Multivariable models were adjusted for sex, age, socioeconomic status, education level, body mass index, smoking status, alcohol intake frequency, physical activity, diet pattern, total energy intake, hypertension, diabetes and genetic predisposition. SSBs, ASBs and NJs were mutually adjusted. ASBs, artificially-sweetened beverages; HRs, hazard ratio; NJs, natural juices; PRS, Polygenic Risk Score; SSBs, sugar-sweetened beverages.

depression.[8 21] The conflicting results of the limited prior research may be partly due to population heterogeneity, varying study designs (cross-sectional and prospective), small sample sizes or the measurement of SSBs consumption. In the current study, we found that higher consumption of SSBs was related to an increased risk of depression. In addition, our study provided novel evidence that higher consumption of ASBs was associated with an increased risk of depression. NJs are often consumed as an alternative to SSBs, and few extensive prospective studies have examined their effect on depression risk to date. A randomised controlled trial involving 40 participants aged 20–30 years found that orange juice consumption was associated with a potential improvement in depression.[22] Another short-term interventional study also demonstrated similar results, with blueberry juice consumption reducing the risk of depression.[23] Our study provided prospective evidence that moderate consumption of NJs was associated with a lower risk of depression. These initial analyses of sugary beverage associations require the application of causal inference methods, such as Mendelian randomisation or randomised controlled trials, to further support the direction of these links.

In addition to environmental factors, genetic predisposition also contributes to the development of depression. The construction of PRS offers a quantitative measure of genetic susceptibility and could help effectively predict individuals at high risk of depression. Data from the two large-scale longitudinal studies, including the Netherlands Study of Depression and Anxiety and the Netherlands Twin Registry, showed a significant association between PRS and the incidence of depression as determined by diverse measurement methods.[24] Our findings were consistent with current evidence from a prospective study of 490 780 participants, suggesting that high genetic predisposition was linked to a 1.32-fold increased risk of depression.[15] Our study found that participants with higher consumption of SSBs and ASBs and high genetic predisposition had the highest depression risk; in contrast, those with moderate consumption of NJs and low genetic predisposition had the lowest risk of developing depression. Nevertheless, we detected no statistically significant interaction between genetic predisposition and SSBs, ASBs and NJs, suggesting that these three beverages were associated with the risk of depression regardless of genetic predisposition. Similarly, a prospective study also

Substitution effect	SSBs			ASBs		
with NJs	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	HR (95% CI)	P value
1 unit/day		0.94 (0.89 to 0.99)	0.013		0.89 (0.85 to 0.94)	<0.001
2 units/day		0.88 (0.80 to 0.97)	0.013		0.80 (0.73 to 0.88)	<0.001
3 units/day		0.82 (0.71 to 0.96)	0.013		0.72 (0.62 to 0.83)	<0.001
4 units/day		0.77 (0.63 to 0.95)	0.013		0.64 (0.53 to 0.78)	<0.001
5 units/day		0.73 (0.56 to 0.93)	0.013		0.57 (0.45 to 0.73)	<0.001

Figure 3 Associations of substituting SSBs and ASBs with natural juices in relation to incident depression. Multivariable models were adjusted for sex, age, socioeconomic status, education level, body mass index, smoking status, alcohol intake frequency, physical activity, diet pattern, total energy intake, hypertension, diabetes and genetic predisposition. SSBs, ASBs and natural juices were mutually adjusted. ASBs, artificially sweetened beverages; NJs natural juices; SSBs, sugar-sweetened beverages; .

found no significant interaction between genetic predisposition and sugary beverages on the risk of dementia, which was in accordance with our findings.[25] In summary, our findings have broad implications for dietary recommendations underlying the consumption of sugary beverages.

The World Health Organization recommends a minimum daily fruit and vegetable intake of 400 grams (five servings) to prevent chronic diseases, but only a minority of people in several countries meet this recommendation.[26] Many studies have indicated that NJs could contribute to meeting the recommended daily intake of fruit and vegetables.[27] Thus, NJs may be a healthy alternative to SSBs and ASBs. To our knowledge, our study is the first to examine the effect of replacing SSBs and ASBs with NJs on the incidence of depression. Moreover, the substitution analyses showed that replacing 1 unit/day of SSBs and ASBs with NJs was associated with a 6% and 11% lower risk of depression, respectively. A recent study observed that the risk of dementia was significantly reduced when SSBs were replaced by NJs.[25] In contrast, we found that replacing SSBs with ASBs was related to higher depression risk. Taken together, these findings underlined that NJs were a healthier alternative to SSBs and ASBs and reverse induced adverse health effects.

The precise mechanisms through which SSBs, ASBs and NJs affect depression are not entirely understood, but several pathways have been proposed. SSBs contain large amounts of fructose, which is known to increase corticosterone levels and result in dysregulation of the hypothalamic–pituitary–adrenal axis.[28] SSBs induce increased secretion of proinflammatory cytokines, such as interleukin 6 and tumour necrosis factor-α, leading to the development of depression. Artificial sweeteners that provide sweetness in low-calorie beverages, such as aspartame and sucralose, may contribute to glucose intolerance through intestinal dysbiosis.[29] This glucose intolerance may affect the development or course of depression. Conversely, NJs contain various vitamins, carotenoids, flavonoids and other bioactive compounds that have beneficial effects on depression.[30] However, adverse effects such as high fructose content may offset these potential benefits when consuming a higher intake of NJs. Future studies are warranted to elucidate the mechanisms underlying these findings.

Limitations

The present study's notable strengths include the large sample size, the prospective design with a long follow-up period, and the comprehensive diagnosis from multiple sources. To our knowledge, this is the first study to examine the association of SSBs, ASBs and NJs with the risk of depression. However, our findings should be interpreted with caution, considering some limitations. First, despite the adjustments for multiple potential confounders in our analyses, it is not possible to exclude residual confounding as a partial explanation for the observed results. Second, as with any observational study, potential reverse causality may also exist. However, the overall results are not materially different in the landmark analysis. Third, the factors included in our study were recorded at baseline; therefore, certain baseline factors may have changed over a relatively long follow-up period. In addition, dietary intake was based on 24-hour recall, which may not accurately reflect long-term habitual diet. Future research should further verify the time-varying effects of beverage intake categories as they relate to depression. Fourth, this study's assessment of sugary beverages was simplistic through an interim questionnaire, reducing its accuracy capability. More accurate measurements of the consumption of SSBs, ASBs and NJs are required to verify these associations. Fifth, it remains unknown whether other beverages, such as tea and coffee, are more beneficial substitutes for SSBs and ASBs than NJs. This will be the focus of a future study. Sixth, there is evidence of 'healthy volunteer' selection bias, as participants in the UK Biobank may be healthier than the general population, with an overall participation rate of approximately 5%. Finally, the participants we investigated in the present study were predominantly white Europeans, which limits the generalisability of our findings to different nationalities and ethnicities.

Implications

In this large-scale prospective cohort study, we found that higher consumption of SSBs and ASBs was associated with a higher risk of depression, whereas moderate consumption of NJs was associated with a lower risk of depression. These associations were not significantly modified by genetic predisposition to depression, although causality could not be inferred. We also found that substituting SSBs and ASBs with NJs was associated with a lower risk of depression. Our findings highlight the need to further reduce the consumption of SSBs and ASBs and replace them with healthier alternatives, such as NJs, in order to reduce the risk of depression. Future investigations are warranted to confirm causal association.

Acknowledgements We would like to express our thanks to all the participants and the coordinating team of the UK Biobank for their valuable time, generosity and contributions to the data collection.

Contributors YW conceptualised and designed the study. YW and HY had full access to all data. YC and HY performed the data analysis. YC drafted the manuscript. BS and LZ contributed to the analysis and interpretation of data. DL and MZ contributed to the revision of the manuscript and approved the final draft. All authors contributed to the intellectual content and critical revisions to the drafts of the paper and approved the final version. YW had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. YW accepted full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was supported by National Natural Science Foundation of China (7191010700, 91746205).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. All participants gave written informed consent prior to data collection. UK Biobank has full ethical approval from the NHS National Research Ethics Service (11/NW/0382). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data that support the findings of this study are available from UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

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