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Alcohol, Smoking, and Their Synergy as Risk Factors for Incident Type 2 Diabetes

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Introduction: Smoking has been independently related to an increased risk of Type 2 diabetes, whereas the role of alcohol remains controversial. The joint impact of tobacco and alcohol use on Type 2 diabetes risk is understudied. This study investigated individual and combined effects of smoking and alcohol on Type 2 diabetes risk.

Methods: Data from 110,076 participants in the NutriNet-Santé cohort (2009−2023), who were free from Type 2 diabetes at baseline and with alcohol and smoking data, were analyzed. Multivariable Cox regression models assessed the association of alcohol consumption (<2 vs ≥2 portions/day, <10 vs ≥10 portions/week, grams/day of ethanol) and smoking (never versus former/current smoking) with Type 2 diabetes risk. Combined effects of heavy smoking (≥20 cigarettes/day) and heavy drinking (>8 and >15 portions/week for women and men, respectively) were also evaluated.

Results: Over 7.5 years of follow-up (820,470 person-years), 1,175 Type 2 diabetes cases were identified. Alcohol consumption, including heavy intake, was not significantly associated with Type 2 diabetes risk. People who formerly or currently smoke had a 36% higher risk of Type 2 diabetes than people who have never smoked (hazard ratio=1.36; 95% CI=1.20, 1.53). Those who smoked heavily had over twice the risk of those who smoked lightly or moderately (hazard ratio=2.10; 95% CI=1.46, 3.02). Combined exposure to smoking and heavy alcohol use did not significantly increase Type 2 diabetes risk (hazard ratio=1.11; 95% CI=0.95, 1.29).

Conclusions: These findings support smoking as an independent risk factor for Type 2 diabetes and show that alcohol consumption did not confer protection. The combined effect of alcohol and tobacco use on Type 2 diabetes risk and the mechanisms behind this relationship should be further explored.

Trial registration: This trial is registered at NCT03335644 at ClinicalTrials.gov.

INTRODUCTION

Type 2 diabetes (T2D) is among the top 10 leading causes of death worldwide,[1] with >500 million people living with diabetes in 2021.[2] T2D results from a complex interplay of genetic, environmental, and modifiable behavioral factors,[3] with lifestyle factors playing a key role in its prevention and delaying its progression.[4,5]

Among the lifestyle factors, tobacco and alcohol use have been identified as risk behaviors for many health outcomes, including T2D.[6–9] Indeed, the role of smoking in T2D risk is well documented.[10] It has been reported that people who smoke have a 37% higher risk

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of T2D than people who do not, with a clear dose−response association when comparing those who smoked heavily with those who smoked lightly or moderately.[10,11] Moreover, an increased risk of premature death has been observed in people who smoke with T2D in comparison with that among people who do not.[11] In turn, smoking cessation has been associated with a long-term reduction in T2D risk and mortality.[7,12] Therefore, the WHO strongly advises against smoking.[4]

Whereas the impact of tobacco use on disease onset has been well established,[10] the role of alcohol remains controversial.[8] The evidence has suggested that low-to-moderate alcohol consumption might decrease T2D risk compared with nonconsumption.[8,13,14] However, the putative beneficial effects of ethanol intake seem to be conditioned by alcohol type,[15] age (>40 years), and sex (women),[13,14,16,17] with deleterious effects in cases of heavy chronic consumption (ethanol intake >60 g/d for men; >50 g/d for women).[13,18] Taking this into account, along with the well-documented deleterious health implications, the WHO stated in 2023 that no level of alcohol consumption could be considered safe.[16,19] In this context, some countries have modified their alcohol consumption guidelines.[20] Despite these measures, globally, the European Region continues to have the highest alcohol consumption level, the greatest proportion of people who drink alcohol,[21] and the highest adult smoking prevalence (28%).[22]

Tobacco and alcohol use are often concomitant, with people who drink being more likely to smoke and vice versa.[23] Alcohol use seems to reduce the time to initiate smoking, whereas tobacco use reduces the subjective effects of alcohol, increasing its use.[24] In addition, a mutually reinforcing effect has been observed when alcohol and tobacco are used simultaneously[24] that could lead to alcohol and/or nicotine dependence.[25] It has been suggested that these behaviors could exacerbate their harmful health effects, including cancer development, elevated triglyceride levels, and increased blood pressure.[26−29] Nevertheless, the role of alcohol and tobacco use on disease risk has been mainly studied individually or as part of composite lifestyle scores, whereas their joint effect on the risk of diabetes remains poorly explored.[5,30]

Given the substantial socioeconomic and public health burden of T2D,[31,32] there is an urgency to elucidate the implications of lifestyle factors on T2D incidence. The authors aimed to assess the relationship between alcohol use, smoking, and T2D risk, including their combined effects. The authors hypothesized that excessive alcohol consumption and smoking would independently and synergistically increase T2D risk.

METHODS

Study Population

This prospective analysis is part of the multidisciplinary project MEMORIES focused on metabolic disorders (https://anr.fr/Projet-ANR-21-CE36-0003). The epidemiologic component of MEMORIES is the NutriNet-Santé study, an ongoing web-based cohort (https://etude-nutrinet-sante.fr/) with continuous recruitment, which was launched in France in 2009.[33] By September 2023, >172,000 individuals aged ≥18 years (≥15 years since 2019) from the general population who comprehend written French and have internet access have been enrolled in the study. Full details of the protocol, study design, and eligibility criteria have been published[33] and can also be accessed at www.clinicaltrial.gov (Number NCT03335644). After the provision of electronic informed consent, participants complete an online self-administered set of validated questionnaires on a range of topics such as sociodemographics; lifestyle; anthropometrics; dietary intake; physical activity; and health status, including personal and family medical history, prevalence and incidence of diseases, and medical treatments.[34−37]

Eligible for the present analysis were individuals enrolled in the cohort any time between May 2009 and September 2023 who had data on smoking and alcohol consumption. Participants with prevalent Type 1 diabetes and gestational diabetes or T2D and those who were diagnosed with T2D within the first 6 months after enrollment (n=3,635) were excluded from the analyses. In addition, individuals aged <18 years and those with missing or incomplete data on dietary intake (<2 dietary records) or whose total energy intake was deemed implausible (<500 and >3500 kcal/day)[38] were likewise excluded (n=74,147), leaving a total sample of N=110,076 for this analysis (Appendix Figure 1, available online).

Measures

Alcohol consumption was assessed at enrollment using a validated tool through 3 nonconsecutive 24-hour dietary records (2 weekdays and 1 weekend day),[35,39] which records all food and beverages consumed during the 3 main meals and any other eating occasion in the previous 24 hours. For each type of food and beverage, individuals reported the type and quantity (g or mL) consumed and the commercial brand for industrial products, if available. All dietary data were weighted to account for weekday and weekend consumption. Mean baseline daily alcohol intake (expressed in g/day of ethanol) and energy intake (kcal) were calculated using the NutriNet-Santé food composition table, which includes

≥3,500 different items (including 83 alcoholic beverages).[40] An alcohol portion was established as 10 g of ethanol.[20] The following alcohol exposures were assessed in this study: (1) adherence (yes/no) to the current French guidelines, which recommend <10 portions (standard servings of alcohol) per week or <2 portions/-day of alcohol on days of consumption, with days off[41]; (2) alcohol consumption risk category based on the U.S. National Institute on Alcohol Abuse and Alcoholism definition of light/moderate drinking (<8 drinks/week for women, <15 drinks/week for men) or heavy drinking (≥8 drinks/week for women, ≥15 drinks/week for men) (1 drink=14 g ethanol)[42]; and (3) alcohol intake modeled as a continuous variable (1 g/day and 1 portion/day).

Tobacco smoking was assessed in the self-administered sociodemographic questionnaire.[34] Participants were categorized as never, former, or current smokers. In addition, on the basis of the number of cigarettes smoked per day, individuals who currently smoke were further split into those who smoked lightly or moderately (<20 cigarettes/day) or those who smoked heavily (≥20 cigarettes/day).[10]

To ascertain T2D, participants were to report any health events, medical treatments, or hospitalizations through the annual health status questionnaire or to provide health-related information at any time through the online health status interface. Furthermore, supplementary medical information is collected from the national health insurance system database. In this study, T2D cases were those who self-reported a diagnosis and/or treatment on a single health status questionnaire or those who self-reported a T2D diagnosis on multiple health status questionnaires. All cases of new-onset T2D occurring at any time point between the initial 6-month period after enrollment and September 30, 2023 were considered. Appendix Table 1 (available online) provides a detailed description of case ascertainment.

Additional demographic data were collected at inclusion. Participants provided self-reported data on sex, age, marital status, education, and occupation using a battery of validated questionnaires.[43] BMI (kg/m^2) was calculated on the basis of self-reported height and weight at baseline.[44] Total physical activity and sedentariness were assessed using data from the International Physical Activity Questionnaire-Short Form, which was also completed at the time of enrollment.[36] Spending ≥8 hours/day sitting was considered as sedentary behavior.[45] Information regarding hypertension, dyslipidemia, and family history of diabetes were obtained from the baseline health status questionnaire. Data on mortality were collected through linkage to the French national mortality registry (CépiDC).

In this study, the authors conducted a complete case analysis to maintain consistency with previous research and to avoid potential bias associated with multiple imputation, given the sensitive and potentially nonrandom nature of the exposure variable (alcohol consumption).[46,47] Participants with missing data on any covariables were excluded, except for covariables with >5% missing values (education, physical activity, sedentary time), in which case a not reported category was created. Regarding the socioprofessional category variable, if the value was missing and age was <25 or >60 years, the respective status of student and retired was attributed. Appendix Table 2 (available online) provides covariate details.

Statistical Analysis

General characteristics of the total study sample at baseline and according to T2D status at follow-up were described using mean±SD values obtained with Student *t*-tests for continuous variables and numbers and percentages obtained with chi-square tests for categorical variables.

Interaction between alcohol consumption and smoking with regard to T2D risk was tested. Multivariable Cox proportional hazards models (hazard ratio [HR] with 95% CI) with age as the timescale were computed to assess the relationships between alcohol consumption, smoking status, and the risk of T2D. Participants contributed person-time until T2D diagnosis; last completed questionnaire; death; or September 30, 2023, whichever occurred first. Adherence to the French alcohol consumption guidelines and the never-smoking categories were used as reference categories, respectively. A stepwise modeling approach was used to progressively adjust for confounders, adding variables in theoretically relevant blocks: Model 1 (demographic factors) was adjusted for sex and age. Model 2 (lifestyle and socioeconomic factors) was also adjusted for obesity, physical activity, education, socioprofessional category, number of 24-hour dietary records (continuous), energy intake without alcohol (kcal/d), and family history of diabetes in first-degree relatives. Model 3 (health status) was additionally adjusted for prevalent hypertension and dyslipidemia. Finally, Model 4 was additionally adjusted for mean daily sedentary behaviors. Models 2, 3, and 4 for alcohol consumption and smoking status were further adjusted for smoking status or alcohol intake (g/d). In a supplementary analysis, all models were refit by modeling BMI as a continuous variable.

The association between alcohol intake modeled as 1 g/day or 1 portion/day increment and risk of T2D in the total sample, in alcohol consumers only, and according to smoking status was assessed through Cox models

adjusted for the covariables mentioned earlier. The same statistical approach was used to assess the associations between quantity of alcohol used (light/moderate versus heavy drinking) and smoking (light/moderate versus heavy smoking) and T2D risk. Finally, Cox models were built to examine the joint association between ever smoking and heavy alcohol consumption. For this purpose, participants were divided into 2 categories: high-risk behavior if they were people who formerly or currently smoked and consumed >10 portion/week of alcohol; otherwise, they were included in the low-to-moderate risk behavior category.

To explore potential effect modification, the authors tested 2-way interaction terms between each exposure (alcohol intake and smoking status), the joint alcohol −smoking variable and age (years), sex (men/women),

Table 1. Baseline Sociodemographic Characteristics of the Study Sample According to Diabetes Status at Follow-Up (N=110,076), NutriNet-Santé 2009−2023

Sociodemographic variables	Full sample (N=110,076)	No incident Type 2 diabetes (*n*=108,901)	Incident Type 2 diabetes (*n*=1,175)	*p*-value[a]
Women	79.0 (86,989)	79.2 (86,252)	62.7 (737)	**<0.001**
Age, years	42.9 (14.6)	42.8 (14.6)	54.8 (10.9)	**<0.001**
Age category, years				
<45	55.5 (61,100)	55.9 (60,891)	17.7 (209)	**<0.001**
≥45	44.5 (48,976)	44.0 (48,013)	82.2 (966)	
Educational level				**<0.001**
Less than high school	14.7 (16,169)	14.5 (15,847)	27.4 (322)	
High school or equivalent	20.1 (22,119)	20.0 (21,850)	22.8 (269)	
College, undergraduate degree	27.0 (29,722)	27.0 (29,477)	20.8 (245)	
Graduate degree	32.1 (35,276)	32.1 (35,013)	22.3 (263)	
Not reported	6.1 (6,790)	6.1 (6,714)	6.4 (76)	
Socioprofessional category				**<0.001**
Without a professional activity[b]	6.4 (7,057)	6.4 (7,040)	1.4 (17)	
Manual/blue-collar worker	6.9 (7,604)	6.8 (7,416)	16.0 (188)	
Office work/administrative staff	60.7 (66,832)	60.6 (66,090)	63.1 (742)	
Professional/executive staff	25.9 (28,583)	26.0 (28,355)	19.4 (228)	
Marital status				0.07
Living alone (single, divorced, widowed)	29.6 (32,643)	29.6 (32,322)	27.3 (321)	
Married/cohabiting	70.4 (77,433)	70.3 (76,579)	72.6 (854)	
Physical activity level[c]				**<0.001**
Low	27.2 (30,009)	27.2 (29,656)	30.0 (353)	
Moderate	35.1 (38,720)	35.2 (38,384)	28.6 (336)	
High	19.1 (21,091)	19.1 (20,800)	24.7 (291)	
Not reported	18.4 (20,256)	18.4 (20,061)	16.6 (195)	
Sedentariness, h/d[d]	6.6 (3.2)	6.6 (3.2)	6.4 (3.3)	0.07
Sedentary behaviors[e]				**<0.001**
No sedentary behavior	51.4 (56,634)	51.4 (55,975)	56.0 (659)	
Sedentary behavior	30.1 (33,169)	30.1 (32,849)	27.2 (320)	
Not reported	18.4 (20,273)	18.4 (20,077)	16.6 (196)	
BMI (kg/m^2)	23.6 (4.4)	23.6 (4.3)	29.8 (6.1)	**<0.001**
BMI category				**<0.001**
Underweight (<18.5)	5.4 (5,979)	5.4 (5,973)	0.5 (6)	
Normal weight (18.5−24.9)	65.2 (71,751)	65.6 (71,506)	20.8 (245)	
Overweight (25.0−29.9)	21.0 (23,127)	20.8 (22,691)	37.1 (436)	
Obesity (≥30.0)	8.4 (9,219)	8.0 (8,731)	41.5 (488)	
Prevalent dyslipidemia[f]	12.5 (13,784)	12.2 (13,343)	37.5 (441)	**<0.001**
Prevalent hypertension	11.8 (13,011)	11.4 (12,493)	44.7 (519)	**<0.001**
Family history of diabetes	17.0 (18,769)	16.7 (18,279)	41.7 (490)	**<0.001**
Energy intake without alcohol, Kcal/d	1,826.5 (458.2)	1,825.7 (457.6)	1,906.1 (502.8)	**<0.001**

(*continued on next page*)

Table 1. Baseline Sociodemographic Characteristics of the Study Sample According to Diabetes Status at Follow-Up (N=110,076), NutriNet-Santé 2009–2023 (*continued*)

Sociodemographic variables	Full sample (N=110,076)	No incident Type 2 diabetes (*n*=108,901)	Incident Type 2 diabetes (*n*=1,175)	*p*-value[a]
Number of 24-hour dietary records	2.9 (0.3)	2.8 (0.3)	2.9 (0.2)	**<0.001**
Alcohol use, g ethanol/d	7.3 (11.0)	7.3 (11.0)	9.6 (13.5)	**<0.001**
Smoking status				
Never smoked	50.2 (55,327)	50.4 (54,888)	37.3 (439)	**<0.001**
Ever smoked	32.6 (35,967)	32.4 (35,386)	49.4 (581)	
Current smoked	17.0 (18,782)	17.1 (18,627)	13.1 (155)	
Risk behavior (joint substance use)[g]	11.5 (12,637)	11.4 (12,422)	18.3 (215)	**<0.001**

Note: Boldface indicates statistical significance ($p<0.05$).
Data expressed as percentage (number) or mean±SD, as appropriate.
[a]Obtained by Pearson's chi-square test for categorical variables or Student *t*-test for continuous variables.
[b]Without professional activity includes homemaker, disabled, unemployed, retired, or student.
[c]Assessed with the International Physical Activity Questionnaire-Short Form; scoring followed established protocol.
[d]Assessed as the number of hours spent sitting daily. This variable had 18.4% of missing values.
[e]Established as <8 hours versus ≥8 hours spent sitting daily.
[f]Determined by the presence of prevalent hypertriglyceridemia and hypercholesterolemia.
[g]Participants were categorized in high-risk behavior if they were people who formerly or currently smoked, and their alcohol consumption was >10 portions/week. Otherwise, they were included in the low/moderate-risk behavior group.

obesity (yes/no), and sedentary behavior (yes/no). All analyses were performed using Stata/SE software (Version 14.0) (StataCorp LP, College Station TX), and a 2-tailed $p<0.05$ was deemed statistically significant.

RESULTS

A total of 110,076 participants (79.2% women, mean age=42.9±14.6 years) were included in the present analyses. During a median follow-up of 7.5 years (IQR=3.1–11.5 years; 820,470 person-years), 1,175 incident cases of T2D were identified. In the total sample, the mean alcohol intake was 7.3±11.0 g/day, and 49% of the volunteers had ever smoked cigarettes. Table 1 displays the sociodemographic characteristics of the participants according to T2D status at follow-up. At baseline, individuals who later developed T2D were more likely to be men, older, less educated, and with higher BMI than their T2D-free counterparts. They also had higher intakes of energy and alcohol and a higher prevalence of comorbidities and family history of diabetes. In the total sample, 10.4% showed a heavy drinking pattern (mean± SD alcohol intake= 31.9±15.8 g/day). In turn, 2.1% of the studied population smoked heavily. The interaction tests between age, sex, BMI, and sedentary behavior and categories of alcohol consumption and smoking status were not significant (all $p>0.05$). Appendix Table 3 (available online) summarizes the baseline characteristics by alcohol consumption and smoking categories. The interaction tests between alcohol consumption and smoking regarding T2D risk were likewise not statistically significant ($p>0.3$).

The results from the Cox models did not demonstrate a significant association between alcohol intake and T2D incidence in the full sample or among alcohol consumers (Table 2 and Appendix Table 4, available online). No significant T2D risk differences were identified between individuals who reported heavy drinking (>8 and 15 portions/week as respective cutoffs for women and men) and those who reported light/moderate drinking. Furthermore, no significant associations were detected when the associations between alcohol consumption (g/day) and risk of T2D were tested separately by smoking status (never versus ever smoking) (Appendix Tables 4 and 5, available online).

Next, people who formerly or currently smoke showed a significantly higher T2D risk than those who had never smoked (Table 3). Compared with individuals who smoked lightly or moderately, those who smoked heavily (≥20 cigarettes/day) showed an increased risk of T2D, even after adjustment for potential confounders (Model 4) (HR=1.64; 95% CI=1.19, 2.25).

In the bivariate analysis, the joint substance use was significantly associated with incident T2D ($p<0.001$) (Table 1). The main results for the association between joint substance use and T2D incidence are presented in Table 4. Individuals categorized in the high-risk behavior group (former/current smoking with alcohol consumption >10 portions/week) did not show a significantly higher risk of developing T2D than individuals in the low/moderate-risk behavior category (HR=1.09; 95% CI=0.93, 1.28). Results remained unchanged when BMI was introduced as a continuous variable.

Table 2. Cox Model Associations (HR; 95% CI) Between Alcohol Consumption and T2D Risk (N=110,076)

	French alcohol consumption guidelines				Alcohol consumption risk categories			
	Portions/week		Portions/day		Total sample N=110,076		Among alcohol consumers *n*=81,329	
	<10[a] adherence	≥10[a] nonadherence	<2[a] adherence	≥2[a] nonadherence	Light/moderate drinking	Heavy drinking[b]	Light/moderate drinking	Heavy drinking[b]
n	92,074	18,002	98,126	11,950	98,583	11,493	69,836	11,493
Alcohol consumption, g/d	**3.47 (3.77)[c]**	**27.24 (14.29)[c]**	**4.27 (4.81)[d]**	**32.69 (14.74)[d]**	**4.49 (5.41)[e]**	**31.92 (15.75)[e]**	**6.35 (5.43)[f]**	**31.92 (15.75)[f]**
T2D cases, % (n)	**0.98 (899)[c]**	**1.53 (276)[c]**	**0.98 (962)[d]**	**1.78 (213)[d]**	**1.03 (1,014)[e]**	**1.40 (161)[e]**	**1.02 (710)[f]**	**1.40 (161)[f]**
Model 1	1 (ref)	1.00 (0.87, 1.16)	1 (ref)	1.07 (0.92, 1.25)	1 (ref)	1.02 (0.86, 1.20)	1 (ref)	1.10 (0.92, 1.31)
Model 2	1 (ref)	0.99 (0.86, 1.15)	1 (ref)	1.05 (0.90, 1.23)	1 (ref)	0.99 (0.84, 1.18)	1 (ref)	1.02 (0.86, 1.22)
Model 3	1 (ref)	0.97 (0.84, 1.13)	1 (ref)	1.02 (0.87, 1.20)	1 (ref)	0.97 (0.82, 1.15)	1 (ref)	1.00 (0.84, 1.19)
Model 4	1 (ref)	0.97 (0.84, 1.13)	1 (ref)	1.02 (0.87, 1.20)	1 (ref)	0.98 (0.83, 1.16)	1 (ref)	1.01 (0.85, 1.20)

Note: Boldface indicates statistical significance ($p<0.05$).
Median follow-up time for T2D: total sample=7.5 years (820,470 person-years); among alcohol consumers=7.6 years (619,279 person-years). Cox proportional hazards models with age as timescale were fitted. Model 1 adjusted for sex (men, women) and age (timescale). Model 2 additionally adjusted for obesity (BMI ≥30 kg/m^2, yes/no), physical activity (low, moderate, high, not reported), education (less than high school, high school or equivalent, college/undergraduate degree, graduate degree, not reported), socioprofessional category (without professional activity, manual/office work/administrative staff, professional/executive staff, retired), number of 24-hour dietary records (continuous), energy intake without alcohol (kcal/d), smoking status (never, former, current), and family history of diabetes in first-degree relatives (yes/no). Model 3 additionally adjusted for prevalence of hypertension (yes/no) and prevalence of dyslipidemia (yes/no). Model 4 additionally adjusted for sedentary behavior (<8 hours/≥8 hours).
[a]One portion=10 g of ethanol.
[b]Cutoff points for heavy drinking are defined as ≥8 and ≥15 portions/week for women and men, respectively; 1 portion=14 g of ethanol.
[c,d,e,f]*p*-values<0.001 for the comparison between alcohol consumption categories were obtained by chi-square test.
HR, hazard ratio; T2D, Type 2 diabetes.

Table 3. Cox Model Associations (HR; 95% CI) Between Smoking Status and T2D Risk (N=110,076)

	Smoking status					
	Total sample N=110,076		Total sample N=110,076		Currently smoked *n*=17,679	
	Never smoked	Ever smoked	Light/ moderate smoking (<20 c/d)	Heavy smoking (≥20 c/d)	Light/ moderate smoking (<20 c/d)	Heavy smoking (≥20 c/d)
n	55,327	54,749	107,746	2,330	15,349	2,330
Cigarettes, units/day	**0 (0)**[a]	**2.82 (5.95)**[a]	**0.93 (0.00)**[b]	**23.07 (6.25)**[b]	**6.56 (4.98)**[c]	**23.07 (6.25)**[c]
T2D cases, % (*n*)[a]	**0.79 (439)**[a]	**1.34 (736)**[a]	**1.05 (1,134)**[b]	**1.76 (41)**[b]	**0.72 (111)**[c]	**1.76 (41)**[c]
Model 1	1 (ref)	**1.36 (1.20, 1.53)**	1 (ref)	**2.14 (1.56, 2.92)**	1 (ref)	**2.10 (1.46, 3.02)**
Model 2	1 (ref)	**1.26 (1.12, 1.43)**	1 (ref)	**1.72 (1.25, 2.35)**	1 (ref)	**1.68 (1.16, 2.42)**
Model 3	1 (ref)	**1.25 (1.11, 1.42)**	1 (ref)	**1.66 (1.21, 2.28)**	1 (ref)	**1.56 (1.08, 2.27)**
Model 4	1 (ref)	**1.25 (1.11, 1.42)**	1 (ref)	**1.64 (1.19, 2.25)**	1 (ref)	**1.57 (1.08, 2.29)**

Note: Boldface indicates statistical significance ($p<0.05$).
Median follow-up time for T2D: total sample=7.5 years (820,470 person-years); among alcohol consumers=7.6 years (619,302 person-years); among people who have never smoked=7.5 years (417,527 person-years); and among people who formerly or currently smoked=7.4 years (402,942 person-years). Cox proportional hazards models were fitted. Model 1 adjusted for sex (men, women) and age (timescale). Model 2 additionally adjusted for obesity (BMI ≥30 kg/m^2, yes/no), physical activity (low, moderate, high, not reported), education (less than high school, high school or equivalent, college/undergraduate degree, graduate degree, not reported), socioprofessional category (without professional activity, manual/office work/administrative staff, professional/executive staff, retired), number of 24-hour dietary records (continuous), energy intake without alcohol (kcal/d), alcohol intake (g/d), and family history of diabetes in first-degree relatives (yes/no). Model 3 additionally adjusted for prevalence of hypertension (yes/no) and prevalence of dyslipidemia (yes/no). Model 4 additionally adjusted for sedentary behavior (<8 hours/≥8 hours).
[a,b,c]*p*-values<0.001 for the comparison between smoking categories were obtained by chi-square tests.
HR, hazard ratio; T2D, Type 2 diabetes.

Table 4. Cox Model Associations (HR; 95% CI) Between Joint Substance Use and T2D Incidence (*n*=110,081)

	Risk behavior	
	Low/moderate risk behavior	High-risk behavior
n	97,443	12,638
T2D cases, % (*n*)[a]	0.99 (960)	1.70 (215)
Alcohol consumption, g/d	4.64 (6.67)	28.3 (15.0)
Model 1	1 (ref)	1.11 (0.95, 1.29)
Model 2	1 (ref)	1.11 (0.95, 1.30)
Model 3	1 (ref)	1.08 (0.92, 1.27)
Model 4	1 (ref)	1.09 (0.93, 1.28)

Note: Participants were categorized in the high-risk behavior if they were people who formerly or currently smoked, and their alcohol consumption was >10 portions/week. Otherwise, they were included in the low/moderate-risk behavior group.
Median follow-up time for T2D was 7.5 years (820,470 person-years). Cox proportional hazards models were fitted. Model 1 adjusted for sex (men, women) and age (timescale). Model 2 additionally adjusted for obesity (BMI ≥30 kg/m^2, yes/no), physical activity (low, moderate, high, not reported), education (less than high school, high school or equivalent, college/undergraduate degree, graduate degree, not reported), socioprofessional category (without professional activity, manual/office work/administrative staff, professional/executive staff, retired), number of 24-hour dietary records (continuous), energy intake without alcohol (kcal/d), and family history of diabetes in first-degree relatives (yes/no). Model 3 additionally adjusted for prevalence of hypertension (yes/no) and prevalence of dyslipidemia (yes/no). Model 4 additionally adjusted for sedentary behavior (<8 hours/≥8 hours).
[a]$p<0.001$ between risk behavior categories was obtained by chi-square test.
HR, hazard ratio; T2D, Type 2 diabetes.

DISCUSSION

In this large population-based cohort study, the individual and joint association of alcohol intake and smoking with T2D risk was explored. A significantly increased risk of T2D was observed for individuals who have ever smoked versus those who have never smoked, which was shown to be even stronger in those who currently smoke heavily. However, alcohol consumption was not significantly associated with T2D incidence. Likewise, there was a nonsignificant T2D risk associated with the combined substance use exposure, that is, ever smoking and heavy alcohol use in the fully adjusted analysis.

Although the harms of alcohol consumption are well documented, this analysis did not find an increased risk of T2D associated with baseline alcohol use, regardless of the alcohol measure applied. Results from a systematic review and meta-analysis suggested that in comparison with abstainers, a reduction in the risk of T2D was present at alcohol intake <63 g/day, with risks increasing above this threshold.[8] However, the authors emphasized that the reductions in risk may have been overestimated in studies that used a reference group including individuals who used to drink. This association has been reported particularly in adults aged >40 years.[8,14] In this study, there was no significant interaction between age and alcohol use with regard to T2D risk.

The lack of statistical significance of the results regarding alcohol use could be partly explained by the sample characteristics, that is, primarily middle-aged women with a relative low mean alcohol intake (7.3 g/day). Even individuals who drink heavily had a much lower mean alcohol intake (31.9 g/day) than the amount associated with increased T2D risk (63 g/day). This observation, in addition to the absence of data on lifetime abstainers, might have contributed to the null findings regarding alcohol. Finally, it should be noted that in Mediterranean countries, alcohol consumption is commonly associated with meal times, and a previous study conducted in individuals free of T2D at baseline observed that currently drinking with moderate alcohol consumption (especially wine) with meals was associated with a lower risk of T2D.[15] Given that this study did not have any specific hypotheses about the type of alcoholic beverage, future research could shed more light on the role of wine versus hard liquor in T2D onset. Consistent with these findings, the results of a previous meta-analysis showed a null association between any level of alcohol consumption and T2D among men.[8]

Findings in this study regarding smoking are consistent with previous reports and support smoking cessation for T2D prevention.[4] Research to date has shown that people who smoke have a 44% higher risk of T2D than individuals that do not smoke[9] and that the risk for those who smoke heavily (≥20 cigarettes/day) is higher (RR=1.61; 95% CI=1.43, 1.80) than the risk for individuals who smoke lightly (RR=1.29; 95% CI=1.13, 1.48).[9] The proposed mechanisms behind these relationships include the effects of nicotine on endothelial dysfunction and sympathetic nervous system stimulation, leading to increases in cortisol and growth hormone secretion and resulting in insulin resistance, higher triglycerides, and lower high-density lipoprotein levels.[48]

To the best of the authors knowledge, this prospective study was the first to investigate concurrent high-risk alcohol consumption and smoking on T2D risk. These findings did not support the hypothesis that combined smoking and alcohol use significantly increased T2D risk, even with heavy or high-risk consumption. Results from a previous systematic review and meta-analysis showed that individuals who smoke with low−moderate alcohol consumption (0−24 g/day) exhibited a reduced risk of T2D compared with individuals who do not smoke. In addition, the protective effect of light alcohol consumption on the risk of T2D was reported to be stronger in individuals who smoke than in individuals who have never smoked.[14]

Whereas smoking has been related to glucose dysregulation and insulin resistance, progressive DNA damage, chronic inflammation, and oxidative stress,[48] low alcohol intake has been associated with the reduction of systemic inflammatory mediators, high-density lipoprotein cholesterol synthesis, reduced fasting insulin, and reduced HbA1c levels.[8,26,49] It may be possible that the alcohol consumption effects on the metabolic response might modulate the adverse effects of tobacco use on T2D risk.

Limitations

This study has several strengths, including its prospective design, 7-year follow-up, large and diverse sample, and adjustment for numerous confounders. However, study findings should be interpreted with caution owing to its limitations: First, the Nutrinet-Santé cohort consists mostly of women (77%), with only around 6% of participants exceeding the recommended alcohol limits, compared with 68.1% of individuals who drink heavily being male in the National Health Barometer 2020 survey.[50] Second, alcohol consumption, often episodic, may not be fully captured by dietary records and may have varied over time, whereas self-reported alcohol consumption may be underestimated owing to reporting bias.[51,52] Third, it has been reported that in the NutriNet-Santé cohort, T2D incidence might be somewhat under-represented in comparison with the general French population.[53] Fourth, although BMI was treated as a confounder, it might also act as a mediator, which merits future investigations. Next, the exclusion of participants with missing data might have introduced selection bias. Finally, data on E-cigarette use and lifetime alcohol abstainers were unavailable.

CONCLUSIONS

The results of this study provide further evidence for smoking as an independent risk factor for T2D and do not support alcohol use for T2D prevention. Although the combined exposure to smoking and heavy alcohol use showed no significant association with T2D risk, this relationship and its mechanisms require further investigation, especially in at-risk populations.

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MD (health event validator and cohort coordinator). Finally, the authors especially thank all volunteers in the NutriNet-Santé cohort. The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines. It was approved by the IRB of the French Institute for Health and Medical Research (INSERM Number 00000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL Number 908450 and Number 909216). NutriNet-Santé is registered (Number NCT03335644) at www.clinicaltrials.gov. Electronic informed consent was obtained from all participants included in the study. Researchers at public institutions can submit a project collaboration request that includes information about their institution and a brief description of the project to collaboration@etude-nutrinet-sante.fr. All requests are reviewed by the steering committee of the NutriNet-Santé study. In case of approval, a signed data-access agreement will be requested, and additional authorizations from the competent administrative authorities may be needed regarding human subjects' data protection. In accordance with existing regulations, no personally identifiable data will be made available.

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SUPPLEMENTAL MATERIAL

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