



Type 2 diabetes in midlife and risk of cerebrovascular disease in late

Abbre iations

(STR), which was added in 1960 [26]. In 1998–2002, a total of 1,173 (≥40 years of age, i.e. born before 1958) were included in the epidemiological study of the Salt Lake County Area Life and Death Study (SALT), a follow-up study of the general population of Salt Lake County, Utah. Of 44,919 individuals aged 60 years and older at the start of the study (before 1954), 417 had died before 31 December 2014, 773 had been diagnosed with type 2 diabetes before the age of 60 years, 4210 had been diagnosed with type 2 diabetes, and 1114 had been diagnosed with type 1 diabetes. A total of 33,086 individuals were included in the study (Fig. 1).

Data collection Information on demographic (age, sex and education), lifestyle (smoking, alcohol consumption), anthropometric (height and weight), and clinical (fasting glucose and HbA_{1c}) data were obtained from the SALT study [26]. Education was defined as the highest level of schooling completed, and dichotomized as <8 years (high school or less) and ≥8 years (college or more). BMI was calculated as weight (kg) divided by height squared (m²), and categorized as <20 kg/m² (underweight), 20–24.9 kg/m² (normal weight), 25–29.9 kg/m² (overweight), and ≥30 kg/m² (obese). Smoking status was categorized as never, former or current smoker. Alcohol consumption was categorized as none, moderate or heavy.

Diabetes was defined as a self-reported diagnosis of diabetes or a fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or a hemoglobin A_{1c} level of ≥6.5% (48 mmol/mol).

Information on the prevalence of type 2 diabetes, CBD, hypertension, heart failure, and stroke was obtained from the National Population Research (NPR), which covers the period from 1960 to 2014. Each individual in the NPR is followed up every 5 years. The prevalence of type 2 diabetes (ICD-9) and heart failure (ICD-9) was defined as a diagnosis of type 2 diabetes (ICD-9) or heart failure (ICD-9) from 1969 to 1986, or a diagnosis of type 2 diabetes (ICD-10) or heart failure (ICD-10) from 1987 to 2014. The prevalence of type 1 diabetes (ICD-9) was defined as a diagnosis of type 1 diabetes (ICD-9) from 1969 to 1986, or a diagnosis of type 1 diabetes (ICD-10) from 1987 to 2014.

Information on the prevalence of type 2 diabetes was obtained from the National Population Research (NPR), which covers the period from 1960 to 2014. The prevalence of type 2 diabetes (ICD-9) was defined as a diagnosis of type 2 diabetes (ICD-9) from 1969 to 1986, or a diagnosis of type 2 diabetes (ICD-10) from 1987 to 2014.

Ascertainment of diabetes

Diabetes was defined as a self-reported diagnosis of diabetes or a fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or a hemoglobin A_{1c} level of ≥6.5% (48 mmol/mol).

E10–E14). The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic White population aged 18–79 years was 10.1% in 2000, 11.1% in 2005, and 12.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Black population aged 18–79 years was 14.1% in 2000, 15.1% in 2005, and 16.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the Hispanic population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Asian population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Pacific Islander population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic American Indian or Alaska Native population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Native Hawaiian or Other Pacific Islander population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Other race population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Unknown race population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic White population aged 18–79 years was 10.1% in 2000, 11.1% in 2005, and 12.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Black population aged 18–79 years was 14.1% in 2000, 15.1% in 2005, and 16.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the Hispanic population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Asian population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Pacific Islander population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic American Indian or Alaska Native population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Native Hawaiian or Other Pacific Islander population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Other race population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010. The age-adjusted prevalence of diagnosed diabetes among the non-Hispanic Unknown race population aged 18–79 years was 11.1% in 2000, 12.1% in 2005, and 13.1% in 2010.

Table 1 Characteristics of the 2 diabetes-free (age 40–59 years) (n=33,086)

Characteristic	T2DM-free n = 31 838	Metformin T2DM n = 1248	p value
Age (years), mean (SD)	60.8 (10.3)	58.5 (8.5)	<0.001
Male, n (%)	14,244 (44.7)	725 (58.1)	<0.001
Education, n (%)			0.934
<8 years	11,619 (36.5)	454 (36.4)	
≥8 years	20,219 (63.5)	794 (63.6)	
Marital status, (%)			0.175
Married/cohabiting	22,933 (72.0)	877 (70.3)	
Single	8905 (28.0)	371 (29.7)	
Zingiber, n (%)			0.086
Missing	6323 (19.8)	230 (18.4)	
Diagnosed	21,257 (66.8)	826 (66.2)	
Undiagnosed	4258 (13.4)	192 (15.4)	
BMI, mean (SD)	24.7 (3.3)	27.6 (4.2)	<0.001
BMI, n (%)			<0.001
<20 (underweight)	1847 (5.8)	19 (1.5)	
20–24.9 (normal weight)	16,313 (51.2)	306 (24.5)	
25.0–29.9 (overweight)	11,685 (36.7)	612 (49.0)	
≥30 (obese)	1993 (6.3)	311 (24.9)	
Smoking status, n (%)			<0.001
Never smoked	15,670 (49.2)	532 (42.6)	
Former	9031 (28.4)	388 (31.1)	
Current	7137 (22.4)	328 (26.3)	
Alcohol consumption, n (%)			<0.001
Never consumed alcohol	29,649 (93.1)	1091 (87.4)	
Paternal/uncle factor	2189 (6.9)	157 (12.6)	
Heart failure, n (%)	8468 (26.6)	517 (41.4)	<0.001
Hypertension, n (%)	8454 (26.6)	693 (55.5)	<0.001

T2DM, type 2 diabetes-free

CI 0.90, 2.84) and 0.96 (95% CI 0.51, 1.80), respectively (Table 4).

Table Characteristics of the 2 diabetes-free CBD (n=1248)

Characteristic	N CBD n=1099	CBD n=149	p value
Age, mean (SD)	57.6 (8.2)	65.1 (7.3)	<0.001
Male, n (%)	644 (58.6)	81 (54.4)	0.325
T2DM-free age, mean (SD)	52.8 (5.2)	52.4 (4.7)	0.361
T2DM diagnosis, median (IQR)	17.8 (9.2)	18.3 (8.3)	0.534
T2DM-free, n (%) ^a			0.268
Diagnosed	106 (13.0)	10 (7.1)	
Older age, diagnosed	117 (14.3)	22 (15.6)	
Individual	36 (4.4)	7 (5.0)	
Combined diagnosis	558 (68.3)	102 (72.3)	

^a290 (23.2%) individuals had diagnosed T2DM-free (IQR, median age; T2DM-free diabetes-free)

The difference in OR for the GEE model was not statistically significant (adjusted: OR 1.03 [95% CI 0.67, 1.50; p=0.897]; unadjusted: OR 0.94 [95% CI 0.62, 1.39; p=0.780]). Because the effect of the GEE model was not statistically significant, we conducted a sensitivity analysis using the GEE model. The effect of the GEE model was not statistically significant (adjusted: OR 1.03 [95% CI 0.67, 1.50; p=0.897]; unadjusted: OR 0.94 [95% CI 0.62, 1.39; p=0.780]).

Supplementary analysis Characteristics of the 2 diabetes-free CBD (n=1248) are presented in Table 1. The characteristics of the 2 diabetes-free CBD are similar to those of the 2 diabetes-free individuals (OR 2.70 [95% CI 2.34, 3.11]), especially for the additional adjustment. The effect of the GEE model was not statistically significant (adjusted: OR 2.70 [95% CI 2.34, 3.11]; unadjusted: OR 2.70 [95% CI 2.34, 3.11]).

Table 3 OR and 95% CI for the association of the following variables with incident T2DM (GEE)

CBD	N	OR (95% CI) ^a	OR (95% CI) ^b	OR (95% CI) ^c
All	3121	1.81 (1.50, 2.19)	1.72 (1.42, 2.08)	1.26 (1.04, 1.53)
Continuous	2190	1.91 (1.54, 2.38)	1.78 (1.43, 2.22)	1.29 (1.03, 1.61)
Occasional	258	2.73 (1.64, 4.55)	2.74 (1.54, 4.60)	2.03 (1.20, 3.44)
Never	540	0.97 (0.59, 1.61)	0.96 (0.58, 1.60)	0.74 (0.44, 1.23)
Substance use	92	0.68 (0.17, 2.78)	0.74 (0.18, 3.07)	0.52 (0.12, 2.21)
Intermittent	448	1.04 (0.61, 1.79)	1.01 (0.59, 1.73)	0.78 (0.45, 1.36)
Unaffected	133	2.18 (1.04, 4.53)	2.26 (1.11, 4.64)	1.78 (0.87, 3.66)

^aAdjusted for age, sex and education

^bAdjusted for age, sex, education, BMI, smoking and alcohol

^cAdjusted for age, sex, education, BMI, smoking, alcohol, and incident T2DM, substance use

category, and the effect of the following variables (ESM Table 2).

Discussion

In this age-cohort study, we found that the incidence of T2DM was higher in individuals who used substances compared to those who did not. This association remained significant after adjusting for age, sex, education, BMI, smoking, and alcohol. The association was particularly strong for individuals who used substances frequently. The association was also observed in individuals who used substances occasionally, but it was not statistically significant. The association was not observed in individuals who used substances intermittently or who were unaffected by substance use.

Table 4 OR and 95% CI for the association between incident T2DM and substance use (GEE)

Continuous	T2DM	
	T2DM-free	T2DM
T2DM-free	801	32
T2DM	19	7
Basic-adjusted OR (95% CI) ^a	1.60 (0.90, 2.84)	
Model-adjusted OR (95% CI) ^b	0.96 (0.51, 1.80)	

The 859 substance users who were included in the study had incident T2DM. In 7, 32 had T2DM. In 32, 7 had incident T2DM. In 19, 7 had incident T2DM. In 19, 7 had incident T2DM.

^aAdjusted for age, sex and education

^bAdjusted for age, sex, education, BMI, smoking, alcohol, and incident T2DM, substance use

T2DM, substance use

Incident T2DM was higher in individuals who used substances compared to those who did not. This association remained significant after adjusting for age, sex, education, BMI, smoking, and alcohol. The association was particularly strong for individuals who used substances frequently. The association was also observed in individuals who used substances occasionally, but it was not statistically significant. The association was not observed in individuals who used substances intermittently or who were unaffected by substance use.

Substance use was associated with incident T2DM, independent of age, sex, education, BMI, smoking, and alcohol. The association was particularly strong for individuals who used substances frequently. The association was also observed in individuals who used substances occasionally, but it was not statistically significant. The association was not observed in individuals who used substances intermittently or who were unaffected by substance use.

The association between substance use and incident T2DM was particularly strong for individuals who used substances frequently. The association was also observed in individuals who used substances occasionally, but it was not statistically significant. The association was not observed in individuals who used substances intermittently or who were unaffected by substance use.

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- P blisher's n e S g e Na e e a' e a h ega d d' c- a c a' b' hed a a d' a aff' a' .**