Association between environmental tobacco smoke exposure and risk of type 2 diabetes mellitus in Chinese female never smokers: A population-based cohort study

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Highlights

• This was the first report attempting to explore the association between environmental tobacco smoke (ETS) exposure and the risk of incident type 2 diabetes (T2DM) in a Chinese population cohort.

• Daily ETS exposure was associated with an approximately 23% higher risk of T2DM.

Abstract

Background: Evidence for the association between environmental tobacco smoke (ETS) exposure and the risk of type 2 diabetes mellitus (T2DM) is limited. The aim of this study was to investigate this association in female never smokers.

Methods: We analyzed 28 177 female participants of the China Kadoorie Biobank (CKB) in the Suzhou area, who were never smokers and had no diabetes. ETS exposure was defined as being exposed to other people's tobacco smoke either at home, workplace, or in public places at least 1 d/wk. Cox proportional hazard regression models were used to assess the association between ETS exposure and incident T2DM according to the frequency and duration of ETS exposure.

Results: A total of 774 incident cases of T2DM were identified during a median 7.3-year follow-up. Compared with no ETS exposure, hazard ratios (95% CIs) for all ETS exposure, daily, and ≥14 h/wk ETS exposure were 1.17(1.00-1.37), 1.23 (1.04-1.46), and 1.25 (1.03-1.53), respectively. Moreover, a positive dose-response relationship was observed between ETS exposure level and T2DM (all P <.05 for trend).

Conclusions: This prospective study suggests that ETS exposure increases the risk of T2DM incidence with dose-response relationship in female never smokers. Thus, reducing ETS exposure may help decrease the burden of T2DM in Chinese females.

KEYWORDS

cohort study, environmental tobacco smoke, type 2 diabetes

1 | INTRODUCTION

The number of people with diabetes has been increasing dramatically in the world, particularly in developing countries.1 Global estimates of the prevalence of diabetes among adults were 6.4% (285 million) for 2010 and 7.7% (439 million) for 2030.2 In China, the estimated

age-standardized prevalence of diabetes was 10.9% among adults in 2013.3 Type 2 diabetes mellitus (T2DM) is the most common type of diabetes mellitus, accounting for over 90% of cases.4

Smoking is an important global health problem, which was the second-leading risk factor for mortality and disability-adjusted life years (DALYs) in 2015. There were 933.1 million daily smokers in the world in the same period.5 More than 33% of nonsmokers were exposed to environmental tobacco smoke (ETS), and 603 000 deaths were attributable to ETS exposure in 2004.6 Whether in 1996 or 2010, the prevalence of smoking in China was significantly higher than the global average.7,8 In 2010, there were more than 300 million smokers in China, 740 million nonsmokers were exposed to ETS,9 and about 16.5% of all deaths (1.4 million) were attributable to smoking.10

Growing epidemiological evidence suggests that smoking is associated with an increased risk of T2DM.11 However, available data on the association between ETS and incident T2DM are inconsistent and controversial. In the CARDIA study, Houston TK et al found no significant effect on incident T2DM for never smokers exposed to ETS.12 In the E3N-EPIC study (Etude Epidémiologique auprès des femmesde la Mutuelle Générale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition), the positive association seemed to be restricted to ETS exposure outside the home, and no such association was detected at home.13 Nevertheless, a cross-sectional study showed that screened diabetes was more likely to be found among female never smokers living with currently smoking husbands.14 The racial, economic, and cultural diversities in different countries may have an influence on developing T2DM.15 There is no published report on exploring this association between ETS and the risk of T2DM in a Chinese population cohort at present. The purpose of this study was to investigate whether ETS exposure was associated with T2DM incidence in female never smokers, and the results would provide evidence for public health policy.

2 | METHODS

2.1 | Study population

The China Kadoorie Biobank (CKB) is a large prospective cohort study. Details of the CKB

study have been reported elsewhere.16-18 This study was carried out in Suzhou, one of the 10 areas of CKB. A total of 53 260 adult residents, including 30 898 women, aged 30 to 79 years were enrolled between 2004 and 2008. Participants were followed up for morbidities and mortality every year after the baseline survey. We limited our analysis to female participants because the proportion of never smokers with ETS exposure was 3.8% among male participants, and the number of T2DM incident among them was small (n = 8).

After excluding 241 participants who were lost to follow-up by 31 December 2013, 2480 participants with prior history of cancer (n = 185), coronary heart disease (n = 331), stroke or transient ischemic attack (n = 198), diabetes (n = 1631, who had self-reported diabetes or random blood glucose >11.1 mmol/L or fasting blood glucose >7.0 mmol/L at baseline), and 272 former or current smokers, a total of 28 177 participants were included in the final analysis. The study was approved by the ethics review committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK). All participants provided written informed consent forms before data collection.

2.2 | Data collection

Information of covariates was obtained from the baseline interviews. The standardized questionnaires included demographic characteristics, such as age, gender, marital status, education level, annual household income, family history of chronic disease, etc; lifestyle behaviors, such as smoke status, alcohol consumption, diet, and physical activity level; and personal health and medical history, such as hypertension, diabetes, cancer, menopause status, use of oral contraceptives, etc. Physical examinations included body weight, height, and blood pressure (BP), using calibrated instruments. In addition, in the vast majority of participants, random blood glucose was measured by venous blood samples, and in very few participants (fewer than 1‰) capillary blood was used if they failed in venous blood collection. Once a participant had abnormal blood glucose levels, the measurement was repeated on the next day using capillary blood after fasting for at least 8 hours. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Prevalent hypertension was defined as self-reported hypertension or measured systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.

2.3 | Definition of never smokers and ETS exposure

ETS exposure in never smokers was assessed using the baseline questionnaire. The information regarding active smoke status, ETS exposure status, and frequency and duration of ETS exposure was obtained as follows: a) How often do you smoke tobacco now? b) In the past, how often did you smoke? (never, only occasionally, on most days, daily, or almost daily). The participants who answered "never" to the first two questions were classified as never smokers. c) How frequently are you exposed to other people's tobacco smoke either at home, your workplace, or in public places? (ie, a minimum of 5 consecutive minutes each time; never or almost never, occasionally [<1 time/wk], 1-2 d/wk, 3-5 d/wk, daily, or almost daily). The never smokers who answered "never or almost never" or "occasionally" to the third question were classified as no ETS exposure. The never smokers who selected the last three categories of the third question were classified as ETS exposure and were further asked: d) How long have you been exposed per week? We categorized frequency of ETS exposure into three groups (1-2 d/wk, 3-5 d/wk, and 6-7 d/wk) and duration of ETS exposure also into three groups by its tertiles (0-4 h/wk, 4-14 h/wk, and ≥14 h/wk), excluding six participants who could not specify the duration.

2.4 | Assessment of T2DM

Information on incident T2DM was regularly collected through linkage with the chronic disease and death registries, health insurance databases, the national health insurance system, or by active follow-up.17 About 5% of participants were randomly chosen for resurvey and blood glucose testing every 3-5 years. Those participants who did not match the above databases were followed up by a household survey every year, but no blood tests were performed. Each event was ascertained by scanned copies of medical records, original disease reporting cards, or official death certificates. T2DM patients were adjudicated by trained physicians and were coded as E11 or E14 by the International Classification of Diseases, 10th Revision (ICD-10). We excluded patients with clear non-T2DM in diabetic patients. Since most of our participants were aged over 40 years and the number of non-T2DM patients was very small among the diabetic patients, the misclassification of other types of diabetes was rare.19

2.5 | Statistical analyses

Person-years of follow-up were calculated from the date of baseline examination (2004-2008) until the date of T2DM events, death, or 31 December 2013, whichever occurred first. Baseline

characteristics by status and intensity of ETS exposure were compared by t test, analysis of variance (ANOVA), or chi-square test as appropriate. Cox proportional hazard regression models were used for estimating hazard ratios (HRs) and their corresponding 95% CIs of T2DM incidence associated with ETS exposure with reference to no ETS exposure among never smokers. We adjusted for potential T2DM risk factors in sequential steps: Model 1 adjusted for continuous age at baseline; model 2 further adjusted marital status (married vs unmarried), level of education (high school and above vs lower than high school), annual household income (in Chinese yuan; <20 000, 20 000-35 000, or ≥35 000), alcohol consumption (weekly vs less than weekly), intake frequency of red meat, vegetables, and fruit (daily vs less than daily), and physical activity (continuous metabolic equivalent of task [MET] h/d); model 3 additionally adjusted continuous BMI, family history of diabetes (no vs yes), menopausal status (no vs yes), and use of oral contraceptives (no vs yes); and model 4 additionally adjusted hypertension (no vs yes). The linear trend test was performed by assigning the medians of frequency or duration of ETS exposure and then modeling those as continuous variables in the models. Sensitivity analyses were conducted to examine the robustness of the association by excluding individuals who developed incident T2DM during the first 2 years of follow-up. The statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina), and a two-sided P <. 05 was defined as statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of the study population

A total of 774 incident cases of T2DM were identified during a median 7.3-year follow-up with 202 746 personyears. Tables 1, S1, and S2 illustrate the baseline characteristics of the female never smokers according to the status, frequency, and duration of ETS exposure, respectively. Among the 28 177 female never smokers, the prevalence of ETS exposure was 68.8%, of which 47.6% were exposed daily or almost daily. The distributions of ETS exposure varied according to age, marital status, education level, annual household income, educational level, red meat consumption, fresh fruit consumption, physical activity, BMI, hypertension history, menopausal status, and use of oral contraceptives.

3.2 | ETS exposure status and T2DM incident

The association between ETS exposure status and the risk of T2DM is shown in Table 2. Absolute T2DM incidence rates were 3.881 and 3.788 per 1000 person-years for the categories “no ETS” and “ETS”, respectively. Compared with no ETS exposure, the HR (95% Cis) for ETS exposure was 1.17 (1.00-1.37). The incident rates were not related to the HRs, and this might be due to the significant impact caused by the adjustment for age.

3.3 | The frequency of ETS exposure and T2DM incident

The association between the frequency of ETS exposure and the risk of T2DM is shown in Table 3. Absolute T2DM incidence rates according to frequency of ETS exposure were 3.083, 3.444, and 3.986 per 1000 person-years for study participants reporting 1-2 d/wk, 3-5 d/wk, and 6-7 d/wk, respectively. Compared with no ETS exposure, the HR (95% CIs) for 6-7 d/wk ETS exposure was 1.23 (1.04-1.46). As the frequency of exposure to ETS increased, the risk of T2DM incidence increased accordingly (all P <.05 for trend).

3.4 | The duration of ETS exposure andT2DM incident

The association between the duration of ETS exposure and the risk of T2DM is shown in Table 4. AbsoluteT2DM incidence rates according to duration of ETS exposure were 3.767, 3.683, and 3.912 per 1000 person-years for study participants reporting 0-4 h/wk, 4-14 h/wk and ≥14 h/wk, respectively. Compared with no ETS exposure, the HR (95%CIs) for female never smokers who were ≥14 h/wk exposed to ETS was 1.25 (1.03-1.53). Similarly, a positive dose-response relationship was observed between the duration of ETS exposure and T2DM (all P < .05 for trend).

3.5 | Sensitivity analysis

Sensitivity analysis generated similar results by excluding participants who developed incident T2DM during the first 2 years of follow-up (Tables S3-S5). Compared with no ETS exposure, the HRs (95% CIs) for total ETS, daily ETS exposure, and ≥14 h/wk ETS exposure were 1.22 (1.02-1.44), 1.28 (1.06-1.53), and 1.32 (1.07-1.63), respectively. And the positive dose-response relationship presented statistically significant (all P <. 05 for trend).

4 | DISCUSSION

In this study in Suzhou, China, we found that ETS exposure was associated with an increased incidence of T2DM in a dose-response relationship in female never smokers, even after

adjustment for multiple confounders. The harmful health effects of ETS exposure have been getting considerable attention in recent years.20 ETS was classified as a known human pulmonary carcinogen by the International Agency for Research on Cancer.21 Encouraging tobacco control has become one of the most important strategies to reduce ETS exposure and thereby decrease disease burden.

4.1 | Comparison with other studies and potential mechanism

These findings echo previous prospective studies which were conducted in foreign population. Ko et al carried out a cohort study on the association among 4442 Korean participants who had smoked fewer than 400 cigarettes during their lifetime and suggested ETS exposure was an important risk factor for the development of T2DM.22 The Nurses' Health Study also examined the impact of exposure to ETS on the prevalence of T2DM during 24 years of follow-up (1 539 278 person-years). They found that long-term ETS exposure heightened the risk of T2DM, and the positive association appeared significant dose dependent after controlling for various relevant lifestyle and dietary factors.23 The research conducted by Jiang L et al on ETS exposure, obesity, and risk of T2DM among Californian teachers yielded more interesting findings. The results showed that those who ever lived with a smoker during both childhood and adulthood had significantly higher risk for T2DM than those without any exposure to ETS.24 Two meta-analysis of prospective cohort studies provided further support for the hypothesis that ETS exposure was associated with an increased risk of incident T2DM, despite including fewer than seven studies in each analysis.25,26 Recently, a cross-sectional study indicated ETS exposure during pregnancy to be an independent risk factor for developing gestational diabetes among Chinese women.27 The potential mechanism involved in the development of T2DM through ETS exposure remains unclear. It is well know that insulin resistance and pancreatic beta cell dysfunction play an important role in most cases of T2DM.28 Nicotine, one of the major toxic components of ETS, may directly induce pancreatic injury and disturb insulin receptor sensitivity.29,30 Some researches focused on tumor necrosis factor-alpha (TNF-alpha), which has deleterious effects on both beta cell function and glucose homeostasis and can impair insulin signaling pathways and lead to enhanced insulin resistance.28,31 According to animal models, TNF-alpha and other inflammation markers were significantly increased in the ETS exposure group compared to the

control group, which can inhibit insulin activity.32,33 S. Oba et al also found that ETS exposure is related to diabetic states and insulin secretion and sensitivity.14

4.2 | Strengths and limitations of this study

The present study has several strengths. Firstly, this was a large population-based cohort study with detailed documentation of ETS exposure and known risk factors for T2DM. To the best of our knowledge, it is the first report that attempts to explore the association between ETS exposure and the risk of incident T2DM in a Chinese population cohort, including the frequency and duration of ETS exposure. Secondly, we conducted our study among never smokers excluding former smokers or occasional smokers to minimize the possible confounding effects on T2DM risk. Thirdly, the values of BP, weight, and height were measured rather than self-reported in our cohort, providing more accurate estimates of hypertension and BMI, both of which were high-risk factors for developing T2DM.34

Some limitations of this study deserve attention. The ETS exposure was evaluated once at baseline, whereas the exposure level might have changed over time. Accordingly, the present study possibly underestimated the harmful effect of ETS exposure on the risk of T2DM. In addition, since the identification of incident T2DM in our study mainly depended on the chronic disease and death registries and the health insurance system, some events of asymptomatic T2DM might be undiagnosed. The current study might underestimate T2DM incidence, and such non differential misclassification might induce attenuation of effect estimates.19 Although we had adjusted for several established and potential risk factors for T2DM, confounding effects from other unmeasured factors (eg, neighborhood, socioeconomic status, or proxies) were still residual.

5 | CONCLUSIONS

In summary, this is a large prospective cohort study to provide evidence about association of ETS exposure with the fast-growing burden of T2DM in China. Our findings show that ETS exposure increased the risk of T2DM incidence with a dose-response relationship. Thus, reducing ETS exposure may help decrease the burden of T2DM in Chinese females.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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Table 1. Characteristics of study population by ETS[†] exposure status

Variables	Total (N=28 177)	No ETS[‡] (N=8 786)	ETS (N=19 391)	*P*[¶]
Age *mean ±SD (Years)*	50.8 ±10.3	54.2 ±11.0	49.3 ±9.5	<.0001
Married *n(%)*	25 672 (91.1)	7 290(83.0)	18 382 (94.8)	<.0001
High school and above *n(%)*	1 961 (7.0)	684 (7.8)	1 277 (6.6)	0.0002
Annual household income *n(%) (in Chinese yuan)*				<.0001
<20 000	7 857 (27.9)	3 350 (38.1)	4 507 (23.2)	
20 000-34 999	9 436 (33.5)	2 685 (30.6)	6 751 (34.8)	
≥35 000	10 884 (38.6)	2 751 (31.3)	8 133 (41.9)	
Family history of diabetes *n(%)*	1 575 (5.6)	476 (5.4)	1 099 (5.7)	0.3977
Weekly alcohol consumption *n(%)*	157 (0.6)	46 (0.5)	111 (0.6)	0.6469
Eating daily *n(%)*				
Red meat	5 726 (20.3)	1 492 (17.0)	4 234 (21.8)	<.0001
Vegetables	28 059 (99.6)	8 750 (99.6)	19 309 (99.6)	0.8743
Fruit	5 418 (19.2)	1 873 (21.3)	3 545 (18.3)	<.0001
Physical activity *mean ±SD (MET*[§] h/day*)*	24.8 ±14.3	21.9 ±14.0	26.1 ±14.2	<.0001
Body Mass index *mean ±SD (kg/m^2)*	24.0 ±3.3	23.9 ±3.3	24.0 ±3.2	<.0001
Hypertension	9 575 (34.0)	3 486 (39.7)	6 089 (31.4)	<.0001
Menopause *n(%)*	16 238 (57.6)	6 026 (68.6)	10 212 (52.7)	<.0001
Use of oral contraceptives *n(%)*	4 005 (14.2)	1 130 (12.9)	2 875 (14.8)	<.0001

[†]ETS=environmental tobacco smoke;

[‡]no ETS=never or almost never or occasionally ETS exposure;

[§]MET=metabolic equivalent of task；

[¶]Two-sided P values were derived from T-test for continuous variables and from the Chi-square test for categorical variables.

Table 2. HRs of T2DM according to the ETS exposure status

	No ETS	ETS
Person-years	64 160	138 586
No of incident	249	525
Incidence rate	3.881	3.788
Model 1	1.00	1.23 (1.06-1.44)**
Model 2	1.00	1.21 (1.03-1.42)*
Model 3	1.00	1.17 (1.00-1.38)*
Model 4	1.00	1.17 (1.00-1.37)

ETS=environmental tobacco smoke; no ETS=never or almost never or occasionally ETS exposure; T2DM= type 2 diabetes mellitus.

Incidence rates were per 1000 person years.

Multivariate models were adjusted for: model 1: age (years); model 2: additionally included marital status (married vs. unmarried), level of education (high school and above vs. lower than high school), annual household income (in Chinese yuan, <20 000, 20 000-35 000 or ≥35 000), alcohol consumption (weekly vs. less than weekly), intake frequency of red meat, vegetables and fruit (daily vs. less than daily) as well as physical activity (MET (metabolic equivalent of task) h/days); model 3: additionally included body mass index (kg/m^2), family history of diabetes (no vs. yes), menopause status (no vs. yes) and use of oral contraceptives (no vs. yes); model 4: additionally adjusted hypertension (no vs. yes).

*P<0.05; **P<0.01.

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Table 3. HRs of T2DM[†] according to the frequency of ETS[‡] exposure

	No ETS[§]	ETS			$P_{for\ trend}$
		1-2 days/week	3-5 days/week	6-7 days/week	
No of participants	8 786	1 651	4 327	13 413	-
Person-years	64 160	12 002	30 490	96 094	-
No of incident	249	37	105	383	-
Incidence rate[¶]	3.881	3.083	3.444	3.986	-
Model 1	1.00	0.99 (0.70-1.39)	1.15 (0.91-1.45)	1.29 (1.10-1.52)**	0.002
Model 2	1.00	0.99 (0.70-1.39)	1.13 (0.89-1.42)	1.27 (1.07-1.50)**	0.004
Model 3	1.00	0.97 (0.68-1.37)	1.06 (0.84-1.34)	1.24 (1.05-1.46)*	0.011
Model 4	1.00	0.95 (0.67-1.35)	1.07 (0.84-1.35)	1.23 (1.04-1.46)*	0.011

[†]T2DM= type 2 diabetes mellitus;

[‡]ETS=environmental tobacco smoke;

[§]no ETS=never or almost never or occasionally ETS exposure;

[¶]Incidence rates were per 1000 person years.

Multivariate models were adjusted for: model 1: age (years); model 2: additionally included marital status (married vs. unmarried), level of education (high school and above vs. lower than high school), annual household income (in Chinese yuan, <20 000, 20 000-35 000 or ≥35 000), alcohol consumption (weekly vs. less than weekly), intake frequency of red meat, vegetables and fruit (daily vs. less than daily) as well as physical activity (MET (metabolic equivalent of task) h/days); model 3: additionally included body mass index (kg/m^2), family history of diabetes (no vs. yes), menopause status (no vs. yes) and use of oral contraceptives (no vs. yes); model 4: additionally adjusted hypertension (no vs. yes).

**$P<0.01$.

Table 4. HRs of T2DM[†] according to the duration of ETS[‡] exposure

	No ETS[§]	ETS			$P_{for\ trend}$
		0-4 h/week	4-14 h/week	≥14 h/week	
No of participants	8 786	5 638	6 768	6 979	-
Person-years	64 160	39 823	48 869	49 847	-
No of incident	249	150	180	195	-
Incidence rate[¶]	3.881	3.767	3.683	3.912	-
Model 1	1.00	1.19 (0.97-1.46)	1.20 (0.98-1.45)	1.32 (1.09-1.60)**	0.005
Model 2	1.00	1.16 (0.94-1.43)	1.17 (0.96-1.43)	1.30 (1.07-1.58)**	0.010
Model 3	1.00	1.14 (0.92-1.40)	1.13 (0.93-1.38)	1.25 (1.03-1.52)*	0.030
Model 4	1.00	1.13 (0.92-1.39)	1.13 (0.92-1.37)	1.25 (1.03-1.53)*	0.030

[†]T2DM= type 2 diabetes mellitus;

[‡]ETS=environmental tobacco smoke;

[§]no ETS=never or almost never or occasionally ETS exposure;

[¶]Incidence rates were per 1000 person years.

Multivariate models were adjusted for: model 1: age (years); model 2: additionally included marital status (married vs. unmarried), level of education (high school and above vs. lower than high school), annual household income (in Chinese yuan, <20 000, 20 000-35 000 or ≥35 000), alcohol consumption (weekly vs. less than weekly), intake frequency of red meat, vegetables and fruit (daily vs. less than daily) as well as physical activity (MET (metabolic equivalent of task) h/days); model 3: additionally included body mass index (kg/m^2), family history of diabetes (no vs. yes), menopause status (no vs. yes) and use of oral contraceptives (no vs. yes); model 4: additionally adjusted hypertension (no vs. yes).

*P<0.05; **P<0.01.