Original Article

Longitudinal association between early-life famine exposure and risk of microvascular complications of type 2 diabetes in adulthood: A retrospective cohort in Tianjin, China

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Background and Objectives: Previous studies have linked famine exposure to the incidence of type 2 diabetes (T2D), yet its impact on diabetic microvascular complications (DMC) remains uncertain. This study aims to investigate the longitudinal association between early-life famine exposure and the risk of DMC in adulthood among individuals with T2D. **Methods and Study Design:** A retrospective cohort study was conducted among inpatients with T2D at Tianjin Medical University Chu Hsien-I Memorial Hospital from June 2014 to June 2022. The 2409 participants were divided into five famine exposure groups based on birth years: no exposure group (1962-1965), fetal period exposure group (1959-1961), early-childhood exposure group (1956-1958), mid-childhood exposure group (1953-1955), and late-childhood exposure group (1949-1952). **Results:** Compared with those nonexposed, early-life famine exposure was associated with higher risks of incident overall DMC (HR_{trend} 1.134, 95% CI 1.052-1.223), diabetic retinopathy (DR) (HR_{trend} 1.193, 95% CI 1.100-1.293), and diabetic kidney disease (DKD) (HR_{trend} 1.262, 95% CI 1.117-1.425), but was not associated with diabetic neuropathy ($p > 0.05$). Notably, significant interactions were found between famine exposure and hypertension regarding the risk of DR, and between famine exposure and both and obesity patterns on the risk of DKD (all p for interaction < 0.05). **Conclusions:** Exposure to famine in early life was associated with increased risks of overall DMC, DR and DKD among patients with T2D. Specially, the association of DR was more pronounced in individuals with hypertension, while the association with DKD was stronger among those with hypertension or both general and abdominal obesity.

Key Words: diabetic microvascular complications, Great Chinese Famine, early life, retrospective cohort, type 2 diabetes

INTRODUCTION

Diabetes poses an escalating challenge to public health worldwide. In 2021, over 0.5 billion adults were affected by diabetes, a figure projected to surge to 0.7 billion by 2045.[1] Type 2 diabetes (T2D) accounts for nearly 90% of diabetes cases, with its prevalence rising notably among individuals under 40.[2] Diabetic microvascular complications (DMC), encompassing diabetic retinopathy (DR),

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Electronic supplementary information available. See apjcn.qdu.edu.cn/35_2_231_supp.pdf
Manuscript received 05 October 2025. Initial review completed 31 October 2025. Revision accepted 21 December 2025.
doi: 10.6133/apjcn.202604_35(2).0006

diabetic kidney disease (DKD), and diabetic neuropathy (DN), significantly undermine patients' quality of life, leading to disability and premature mortality.[3, 4] DMC are prevalent in T2D patients; a prospective study across 28 countries, including China, revealed DMC in approximately 50% of T2D patients cases.[5] Moreover, a meta-analysis reported DR prevalence at 18.45% among Chinese individuals with diabetes, a primary cause of avoidable visual impairment and blindness in the working-age population.[6] DKD and DN stand as critical contributors to end-stage renal disease, lower-limb amputation, and disabling neuropathic pain.[7, 8] In China, approximately 20% of T2D patients may develop DKD,[8] while over 60% may develop DN.[9] Thus, preventing DMC in T2D patients is imperative.

The developmental origins of health and disease theory posit that malnutrition in early life induces metabolic alterations to adapt to adverse conditions, potentially heightening the risk of metabolic diseases in adulthood.[10] Evidence from the Great Chinese Famine, the Ukraine famine, and the Dutch Winter famine suggests that individuals exposed to famine in early life may have a higher risk of T2D.[11-13] However, investigations into the associations between famine exposure and DMC, particularly among the Chinese population, remain scarce. To date, only one study involving T2D patients from Ukraine and Hong Kong has indicated an association between perinatal famine exposure and an increased risk of proliferative diabetic retinopathy (PDR).[14] Other studies assessing prenatal nutrition status using birth weight have explored the relationship between birth weight and one or more DMC subtypes.[15, 16]

The Great Chinese Famine, occurring from 1959 to 1961, stands as one of the most severe and extensive famines in human history, affecting most of Chinese mainland.[17] As a natural experiment, famine provides a unique opportunity to investigate the long-term impact of exposure to famine in early life on adult diseases. Therefore, this study aims to elucidate the longitudinal associations of exposure to the Great Chinese famine in different early-life periods with the incidence of overall DMC and its three subtypes (DR, DKD and DR) in adulthood. We seek to provide novel insights and recommendations for DMC prevention strategies.

METHODS

Study population

This retrospective cohort study utilized data from patients hospitalized for T2D at the endocrinology department of Tianjin Medical University Chu Hsien-I Memorial Hospital from June 2014 to June 2022. The entry point was defined as the time of T2D first diagnosis. Follow-up continued until the occurrence of DMC, loss to follow-up, or the study end date (December 31, 2022). The follow-up time was calculated based on the date of T2D first diagnosis to the occurrence date of DMC, the date of loss to follow-up, or the end date of the study. Initially, 10377 individuals born between 1949 and 1965 were identified. Subsequently, 7792 individuals were excluded from the analysis based on the following criteria: missing lifestyle factors data (n = 5014), incomplete Body-mass index (BMI), therapy methods, or hypertension history (n = 292), insufficient blood indicator data (n = 2468), a history of one or more DMC (n = 18), or a history of malignant tumors (n = 18). Ultimately, the analysis included 2409 individuals (Figure 1).

The retrospective cohort study was conducted without interfering with routine diagnosis and treatment, posing no impact on participants' medical rights, and carry no increased risk to participants. The study protocol received approval from the Ethics Committee of Tianjin Medical University Chu Hsien-I Memorial Hospital (approval number: ZXYJNYYhMEC2022-11). Informed consent was waived due to the inability to locate most participants, and the study did not involve personal privacy or commercial interests. All procedures adhered to the principles of the Declaration of Helsinki, and confidentiality was maintained for all participant information included in the study.

Definitions of DMC

Consistent with previous studies,[18, 19] overall DMC were defined as the presence of one or more of the following: DR, DKD, and DN. DR diagnosis relied on dilated fundus examination findings, indicating microaneurysms or more severe manifestation.[20] DKD diagnosis required meeting one or both of the following criteria in diabetic patients, excluding chronic kidney disease (CKD) from other etiologies:[21] (1) persistent estimated glomerular filtration rate (eGFR) < 60 mL/ min/1.73 m² for over 3 months; (2) urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g or urinary albumin excretion rate ≥30 mg/day confirmed at least twice within 3 to 6 months. DN diagnosis followed the criteria outlined in the "Guideline for the Prevention and Treatment of T2D Mellitus in China (2020 edition)".[22]

Classification of famine exposure groups

The Chinese Famine endured from 1959 to 1961.23 Consistent with previous Chinese famine studies,[24, 25] participants were divided into 5 groups according to their western birthdates: those born between January 1, 1962 and December 31, 1965, comprised the no exposure group; those born between January 1, 1959 and December 31, 1961, constituted the fetal period exposure group; those born between January 1, 1956 and December 31, 1958, formed the early-childhood exposure group; those born between January 1, 1953 and December 31, 1955, represented the mid-childhood exposure group; and those born between January 1, 1949 and December 31, 1952, comprised the late-childhood exposure group.

Classification of obesity patterns

Weight, height, and waist circumference (WC) were measured by nurses. BMI was calculated as weight in kilograms divided by the square of height in meters. General obesity was defined by the BMI, utilizing Chinese-specific cutoff values, with overweight defined as 24 $kg/m^2 \leq$ BMI <28 kg/m^2 and obesity as BMI ≥ 28 kg/m^2.[26] Similarly, abdominal obesity was determined by WC ≥90 cm for males and WC ≥85 cm for females.26 Obesity patterns were categorized into three types: (1) G−/A−: neither general nor abdominal obesity; (2) G+/A− or

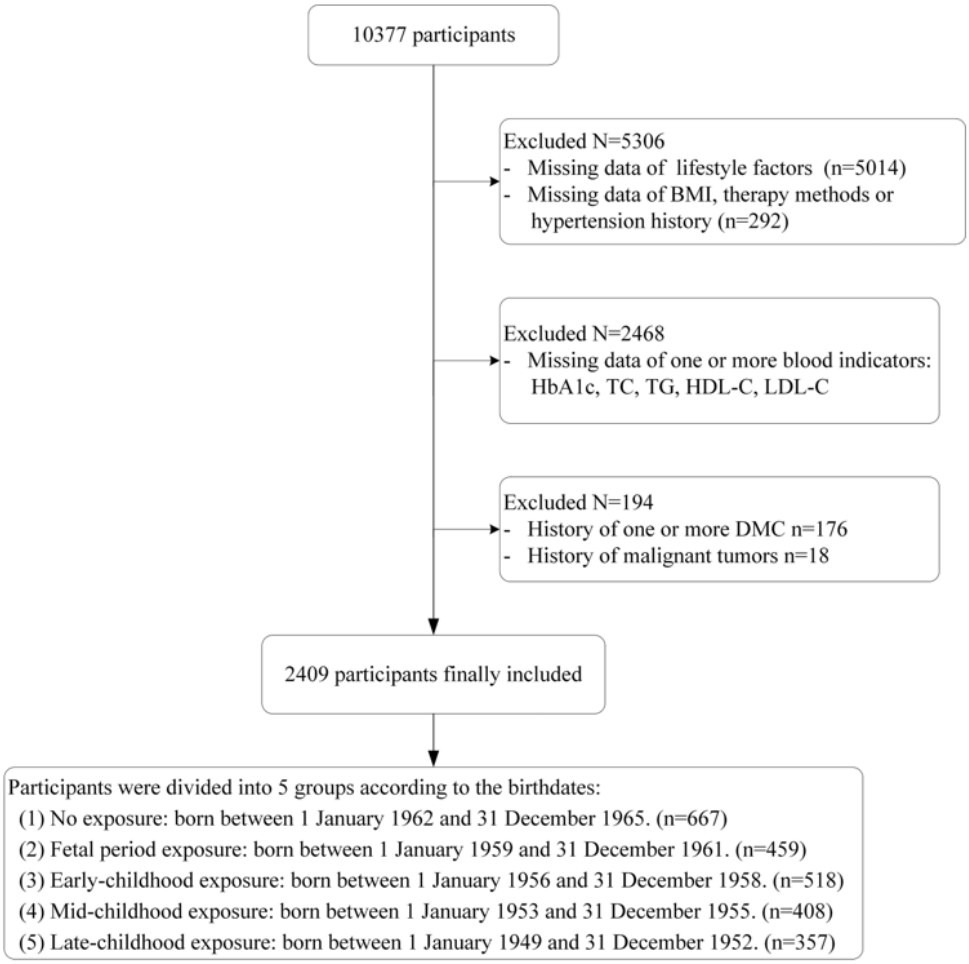

Figure 1. Flow chart of study participants. BMI, body mass index; HbA1c, haemoglobin A1c; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DMC, diabetic microvascular complications

G−/A+: either general or abdominal obesity; (3) G+/ A+: both general and abdominal obesity.

Definitions and measurements of hypertension and microalbuminuria

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg[27] or documented previous hypertension diagnosis in medical records. Blood pressure measurements utilized a standard mercury sphygmomanometer, with a third measurement conducted if the SBP-DBP difference exceeded 10 mmHg. Microalbuminuria (MAU) was defined as 30-300 mg of urinary albumin per 24-hour urine collection,[28] determined via immunoturbidimetry.

Other variables

Basic participant information, including date of birth, age, sex, history of present illness, past medical history, and medical history, was extracted from electronic medical records. Overnight fasting venous blood samples were collected for the assessment of various blood indicators: total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and haemoglobin A1c (HbA1c). Blood indicator results were obtained from the first post-admission assessment.

Statistical analysis

Baseline characteristics were presented as median (P25, P75) for continuous variables and frequencies (percentages) for categorical variables. Continuous variable distribution was assessed using the Kolmogorov-Smirnov normality test. Differences in continuous and categorical variables across famine exposure groups were evaluated using the Kruskal-Wallis H test and chi-square test, respectively. Cox proportional hazard regression was employed to analyze the longitudinal associations of famine exposure with the incidences of overall DMC and its subtypes (DR, DKD, or DN). Time to event was calculated from T2D diagnosis date to first-time DR, DKD, or DN diagnosis or the end of follow-up, whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. MAU serves as a marker of generalized endothelial dysfunction, closely associated with a high risk of cardiovascular and renal diseases in diabetic populations.[29, 30] Consequently, logistic regression was performed to analyze the relationship of famine exposure and MAU status to elucidate famine exposure's effect on microangiopathy. Odds ratio (OR) and 95% CIs were reported.

Three models were constructed: Model 1 adjusted for age (continuous, years) and sex (male or female); Model 2 further adjusted for BMI (continuous, kg/m^2), smoking (no or yes), and drinking (no or yes); Model 3 additionally adjusted for hypertension (no or yes), therapy methods

(lifestyle intervention, oral medicine, insulin, oral medicine and insulin), HbA1c (continuous, %), TG (continuous, mmol/L), and LDL-C (continuous, mmol/L). The proportional hazards assumption of the Cox model was assessed using the Schoenfeld residuals test. The Cox models satisfy the proportional hazards assumption (p >0.05).

Stratified analyses were performed for sex (male, female), hypertension (no, yes), and obesity patterns (G−/A−, G+/A− or G−/A+, G+/ A+). Interactions between famine exposure and stratified factors on outcome risk were examined using multivariable-adjusted Cox models with cross-product terms. Given the ambiguity surrounding the precise onset and conclusion of the Chinese famine spanning 1959 to 1961, and recognizing its gradual nature, it's plausible that individuals born the year before its onset or the year after its conclusion might also have been affected. Therefore, we performed sensitivity analyses by excluding participants born in 1958 and 1962 to minimize exposure misclassification's impact. Considering that disease duration is a major predictor of DMC,[31] we additionally adjusted the disease duration on the basis of Model 3 for sensitivity analysis.

All analyses were performed using SPSS 24.0, with statistical significance set at p <0.05 (two-tailed).

RESULTS

Participants characteristics

A total of 2409 participants were included in this study, comprising 1136 women and 1273 men, with a median age of 61 years. The characteristics of all participants stratified by early-life famine exposure categories are detailed in Table 1. Notably, 459 participants experienced the Great Chinese Famine during the fetal period, while 518, 408, and 357 were exposed during early childhood, middle childhood, and late childhood, respectively. Apart from the evident age disparity across famine exposure groups, significant differences were observed in sex, TC, TG, LDL-C, HbA1c, smoking and alcohol consumption rates, hypertension prevalence. In addition, the characteristics were balanced between the included participants (n = 2409) and excluded (n = 7968) individuals, with no statistically significant differences (all p >0.05) (Supplementary Table 1).

Longitudinal associations of famine exposure with DMC, DR, DKD, and DN

A median overall follow-up time was 13.00 years, the median follow-up time of the no exposure group, fetal period exposure group, early childhood exposure group, middle childhood exposure group and late childhood exposure group were 10.00 years, 13.08 years, 13.04 years, 14.00 years and 14.00 years. No participants died during the follow-up period. A total of 2293 incident cases of DMC were identified, including 1945 cases of DR, 885 cases of DKD, and 1552 cases of DN. Table 2 displays the longitudinal associations of famine exposure with the incidence of overall DMC and its subtypes, as determined by Cox proportional hazard regression models applied to all participants across three models. Compared to participants without famine exposure, those exposed during childhood had 28.6% (HR 1.286, 95% CI 1.069-1.548 in early-childhood), 31.6% (HR 1.316, 95% CI 1.029-1.684 in mid-childhood), and 67.3% (HR 1.673, 95% CI 1.226-2.283 in late-childhood) higher risks of incident overall DMC after adjusting for all covariates. A higher risk of DR was evident among participants exposed to famine during any period, with 20.7%, 55.9%, 64.8% and 104.4% higher risks in those with fetal exposure (HR 1.207, 95% CI 1.027-1.418), early-childhood exposure (HR 1.559, 95% CI 1.276-1.905), mid-childhood exposure (HR 1.648, 95% CI 1.261-2.153), and late-childhood exposure (HR 2.044, 95% CI 1.458-2.866). Similarly, participants with childhood famine exposure had 61.8% (HR 1.618, 95% CI 1.197-2.187 in early-childhood), 77.2% (HR 1.772, 95% CI 1.187-2.645 in mid-childhood), and 159.2% (HR 2.592, 95% CI 1.565-4.294 in late-childhood) higher risks of DKD. These associations remained significant across all models. Besides, our analysis revealed a significant association between childhood famine exposure and an increased risk of MAU, mirroring the findings observed for overall DMC and DKD (n = 1359, Supplementary Table 2). However, no significant association was observed between famine exposure and DN in any of the models. Furthermore, trend analysis indicated a gradual increase in the risks of overall DMC, DR, and DKD from the fetal period to late childhood of famine exposure (all p for trend <0.05).

Subgroup analysis

Figure 2 shows the risk of DR across famine exposure categories, stratified by sex, hypertension, and obesity patterns. A significant interaction was identified solely within the hypertension stratum and famine exposure (p for interaction = 0.022), with no notable interactions observed across sex (p for interaction = 0.714) and obesity patterns (p for interaction = 0.087). Relative to unexposed participants, any exposure to famine correlated with 34.6% (HR 1.346, 95% CI 1.112-1.630 in fetal period), 75.8% (HR 1.758, 95% CI 1.388-2.226 in early-childhood), 77.0% (HR 1.770, 95% CI 1.291-2.427 in mid-childhood) and 112.8% (HR 2.128, 95% CI 1.428-3.171 in late-childhood) elevated risks of DR development among individuals with hypertension, whereas no such association was observed in those without hypertension.

The associations between DKD and famine exposure, stratified by sex, hypertension, and obesity patterns, are shown in Figure 3. Except for sex (p for interaction = 0.744), both hypertension (p for interaction = 0.020) and obesity patterns (p for interaction = 0.021) demonstrated significant interactions with famine exposure. Compared to unexposed groups, 39.0%, 83.7%, 88.2% and 171.4% increased risks of DKD were significantly associated with fetal (HR 1.390, 95% CI 1.049-1.842) and childhood (HR 1.837, 95% CI 1.296-2.604 in early-childhood; HR 1.882, 95% CI 1.183-2.994 in mid-childhood; HR 2.714, 95% CI 1.514-4.865 in late-childhood) famine exposure in the hypertension group, but not in the non-hypertension group. Participants exhibiting G+/A+ obesity patterns displayed 85.6%, 200.6% and 322.7% incremental DKD risks with exposed to famine during fetal life (HR 1.856, 95% CI 1.112-3.099), early-childhood (HR 3.006, 95% CI 1.572-5.746) and late-childhood (HR 4.227, 95% CI

Table 1. The characteristics of all participants

Variables	Total (n = 2409)	No exposure (n = 667)	Fetal period exposure (n = 459)	Early-childhood exposure (n = 518)
Age, median (P_{25}, P_{75})	61.0 (58.0, 65.0)	56.0 (55.0, 57.0)	60.0 (58.0, 61.0)	62.0 (61.0, 63.0)
BMI, median (P_{25}, P_{75}), kg/m^2	25.8 (23.7, 28.2)	26.0 (23.9, 28.4)	25.7 (23.6, 28.0)	25.6 (23.5, 28.3)
Sex, n (%)				
Male	1273 (52.8)	396 (59.4)	242 (52.7)	276 (53.3)
Female	1136 (47.2)	271 (40.6)	217 (47.3)	242 (46.7)
Smoking, n (%)				
No	1401 (58.2)	351 (52.6)	257 (56.0)	297 (57.3)
Yes	1008 (41.8)	316 (47.4)	202 (44.0)	221 (42.7)
Drinking, n (%)				
No	1558 (64.7)	391 (58.6)	279 (60.8)	339 (65.4)
Yes	851 (35.3)	276 (41.4)	180 (39.2)	179 (34.6)
Hypertension, n (%)				
No	642 (26.7)	223 (33.4)	120 (26.1)	141 (27.2)
Yes	1767 (73.4)	444 (66.6)	339 (73.9)	377 (72.8)
Therapy methods, n (%)				
Lifestyle intervention	144 (5.98)	37 (5.55)	23 (5.01)	31 (5.98)
Oral medicine	805 (33.4)	242 (36.3)	148 (32.2)	161 (31.1)
Insulin	262 (10.9)	75 (11.2)	51 (11.1)	58 (11.2)
Oral medicine and insulin	1198 (49.7)	313 (46.9)	237 (51.6)	268 (51.7)
TC, median (P_{25}, P_{75}), mmol/L	4.94 (4.06, 5.81)	5.08 (4.20, 5.94)	4.98 (4.06, 5.89)	4.92 (4.09, 5.85)
TG, median (P_{25}, P_{75}), mmol/L	1.51 (1.09, 2.13)	1.58 (1.13, 2.32)	1.55 (1.11, 2.15)	1.50 (1.08, 2.08)
HDL-C, median (P_{25}, P_{75}), mmol/L	1.12 (0.95, 1.30)	1.11 (0.96, 1.28)	1.14 (0.94, 1.33)	1.13 (0.96, 1.30)
LDL-C, median (P_{25}, P_{75}), mmol/L	3.30 (2.62, 3.97)	3.40 (2.74, 4.05)	3.31 (2.65, 4.04)	3.28 (2.63, 4.02)
HbA_{1c}, median (P_{25}, P_{75}), %	8.50 (7.40, 9.90)	8.60 (7.50, 10.20)	8.40 (7.30, 9.70)	8.50 (7.40, 9.90)

BMI, body mass index; HbA1c, haemoglobin A1c; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol.
$p < 0.05$ indicates statistical significance.

Table 1. The characteristics of all participants (cont.)

Variables	Mid-childhood exposure (n=408)	Late-childhood exposure (n=357)	*p* value
Age, median (P_{25}, P_{75})	65.0 (64.0, 66.0)	68.0 (67.0, 70.0)	<0.001
BMI, median (P_{25}, P_{75}), kg/m^2	25.8 (23.5, 28.0)	26.0 (24.1, 28.4)	0.321
Sex, n (%)			<0.001
Male	194 (47.6)	165 (46.2)	
Female	214 (52.5)	192 (53.8)	
Smoking, n (%)			
No	262 (64.2)	234 (65.6)	<0.001
Yes	146 (35.8)	123 (34.5)	
Drinking, n (%)			
No	290 (71.1)	259 (72.6)	<0.001
Yes	118 (28.9)	98 (27.5)	
Hypertension, n (%)			
No	83 (20.3)	75 (21.0)	<0.001
Yes	325 (79.7)	282 (79.0)	
Therapy methods, n (%)			0.454
Lifestyle intervention	25 (6.13)	28 (7.84)	
Oral medicine	125 (30.6)	129 (36.1)	
Insulin	41 (10.1)	37 (10.4)	
Oral medicine and insulin	217 (53.2)	163 (45.7)	
TC, median (P_{25}, P_{75}), mmol/L	4.85 (3.94, 5.66)	4.73 (3.94, 5.67)	0.001
TG, median (P_{25}, P_{75}), mmol/L	1.42 (1.07, 2.01)	1.47 (1.06, 1.96)	0.003
HDL-C, median (P_{25}, P_{75}), mmol/L	1.12 (0.95, 1.31)	1.10 (0.94, 1.26)	0.674
LDL-C, median (P_{25}, P_{75}), mmol/L	3.21 (2.52, 3.84)	3.12 (2.54, 3.89)	0.002
HbA_{1c}, median (P_{25}, P_{75}), %	8.60 (7.50, 9.90)	8.30 (7.20, 9.55)	0.018

BMI, body mass index; HbA1c, haemoglobin A1c; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol.
$p < 0.05$ indicates statistical significance.

Table 2. The longitudinal association of famine exposure with the incidence of DMC

	Model 1†		Model 2‡		Model 3§	
	HR (95% *CI*)	*p* value	*HR* (95% *CI*)	*p* value	*HR* (95% *CI*)	*p* value
Overall DMC						
Fetal period exposure	1.038 (0.896-1.202)	0.619	1.042 (0.900-1.207)	0.580	1.051 (0.906-1.219)	0.509
Early-childhood exposure	1.324 (1.101-1.592)	0.003	1.323 (1.100-1.591)	0.003	1.286 (1.069-1.548)	0.008
Mid-childhood exposure	1.426 (1.118-1.818)	0.004	1.428 (1.120-1.821)	0.004	1.316 (1.029-1.684)	0.029
Late-childhood exposure	1.915 (1.406-2.608)	<0.001	1.919 (1.409-2.614)	<0.001	1.673 (1.226-2.283)	0.001
Trend test	1.174 (1.090-1.265)	<0.001	1.174 (1.090-1.265)	<0.001	1.134 (1.052-1.223)	0.001
DR						
Fetal period exposure	1.185 (1.011-1.389)	0.037	1.193 (1.017-1.399)	0.030	1.207 (1.027-1.418)	0.022
Early-childhood exposure	1.591 (1.303-1.943)	<0.001	1.594 (1.305-1.947)	<0.001	1.559 (1.276-1.905)	<0.001
Mid-childhood exposure	1.768 (1.359-2.301)	<0.001	1.776 (1.364-2.311)	<0.001	1.648 (1.261-2.153)	<0.001
Late-childhood exposure	2.330 (1.666-3.259)	<0.001	2.338 (1.672-3.271)	<0.001	2.044 (1.458-2.866)	<0.001
Trend test	1.233 (1.138-1.337)	<0.001	1.234 (1.138-1.337)	<0.001	1.193 (1.100-1.293)	<0.001
DKD						
Fetal period exposure	1.104 (0.870-1.402)	0.415	1.126 (0.886-1.431)	0.330	1.174 (0.920-1.497)	0.197
Early-childhood exposure	1.565 (1.161-2.109)	0.003	1.587 (1.177-2.139)	0.002	1.618 (1.197-2.187)	0.002
Mid-childhood exposure	1.781 (1.203-2.636)	0.004	1.800 (1.215-2.666)	0.003	1.772 (1.187-2.645)	0.005
Late-childhood exposure	2.626 (1.596-4.320)	<0.001	2.612 (1.587-4.297)	<0.001	2.592 (1.565-4.294)	<0.001
Trend test	1.272 (1.128-1.435)	<0.001	1.270 (1.126-1.432)	<0.001	1.262 (1.117-1.425)	<0.001
DN						
Fetal period exposure	0.844 (0.707-1.009)	0.063	0.849 (0.710-1.014)	0.071	0.856 (0.715-1.025)	0.091
Early-childhood exposure	0.960 (0.766-1.202)	0.721	0.959 (0.766-1.202)	0.718	0.940 (0.750-1.178)	0.590
Mid-childhood exposure	0.867 (0.644-1.168)	0.349	0.869 (0.645-1.170)	0.354	0.820 (0.606-1.109)	0.197
Late-childhood exposure	1.048 (0.718-1.532)	0.807	1.050 (0.719-1.535)	0.801	0.949 (0.648-1.390)	0.790
Trend test	1.010 (0.922-1.108)	0.824	1.010 (0.922-1.107)	0.828	0.986 (0.899-1.081)	0.762

DMC, diabetic microvascular complications; DR, diabetic retinopathy; DKD, diabetic kidney disease; DN, diabetic neuropathy; BMI, body mass index; HbA1c, haemoglobin A1c; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; HR, hazard ratio.

†Model 1: age and sex were adjusted.

‡Model 2: age, sex, BMI, smoking, and drinking were adjusted.

§Model 3: age, sex, BMI, smoking, drinking, hypertension, therapy methods, HbA1c, TG, and LDL-C were adjusted.

p <0.05 indicates statistical significance.

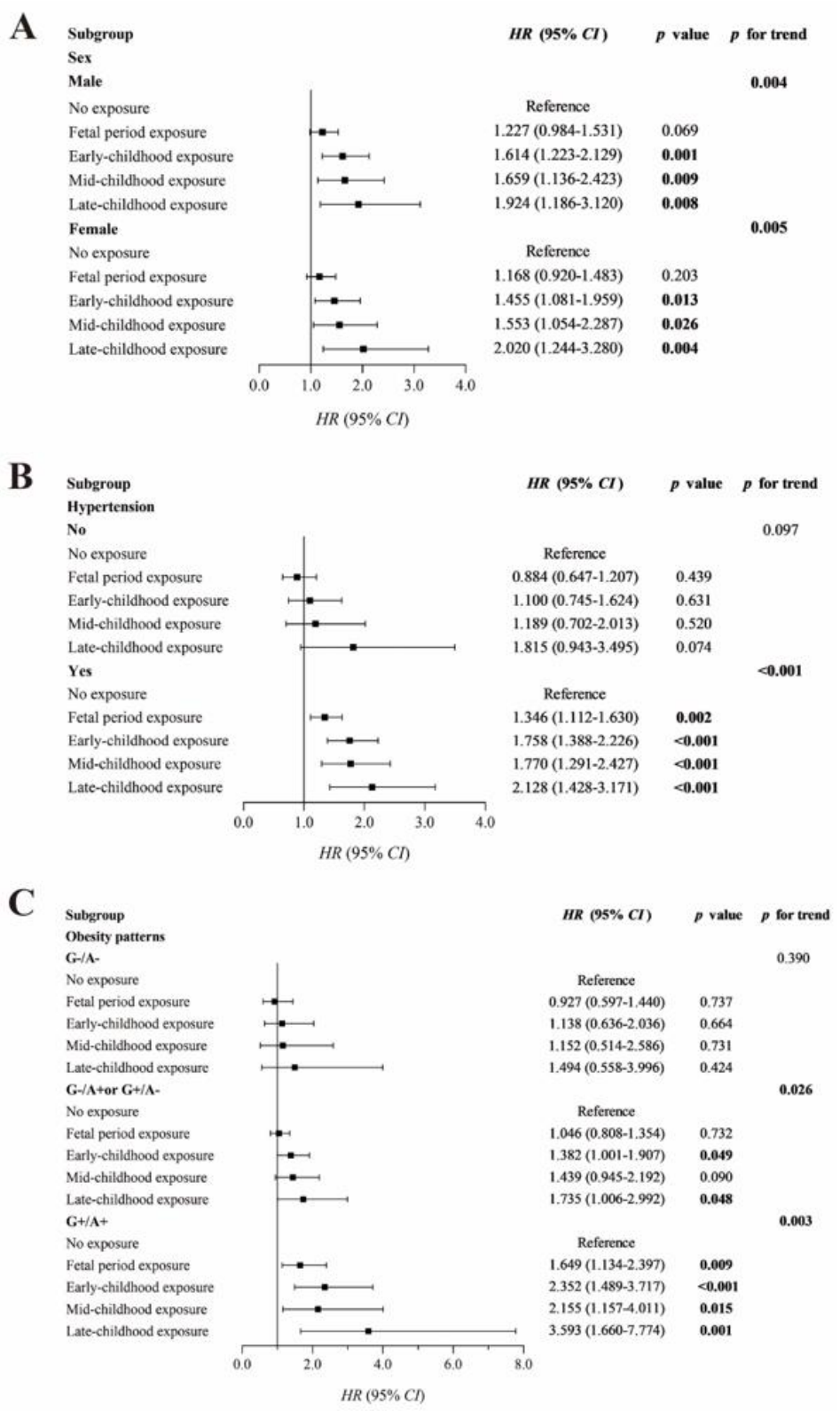

Figure 2 Forest plots of the associations between famine exposure and the incidence of DR according to (a) sex (male = 1273, female = 1136), (b) hypertension (no = 642, yes = 1767), and (c) obesity patterns (G−/A− = 342, G+/A− or G−/A+ = 976, G+/ A+ = 473)
All models adjusted for age, sex, BMI, smoking, drinking, hypertension, therapy methods, HbA1c, TG, and LDL-C; stratification variables were not adjusted in the corresponding analyses. Boldface indicates statistical significance ($p < 0.05$).

1.412-12.655), which were not evident among participants with other obesity patterns.

Additionally, the associations between famine exposure and DN was not significantly modified by any subgroup factors (all p for interaction >0.05) (Supplementary Table 3). Similarly, no significant interactions were observed between the famine exposure and the stratified factors regarding overall DMC incidence (all p for interaction >0.05) (Supplementary Table 4).

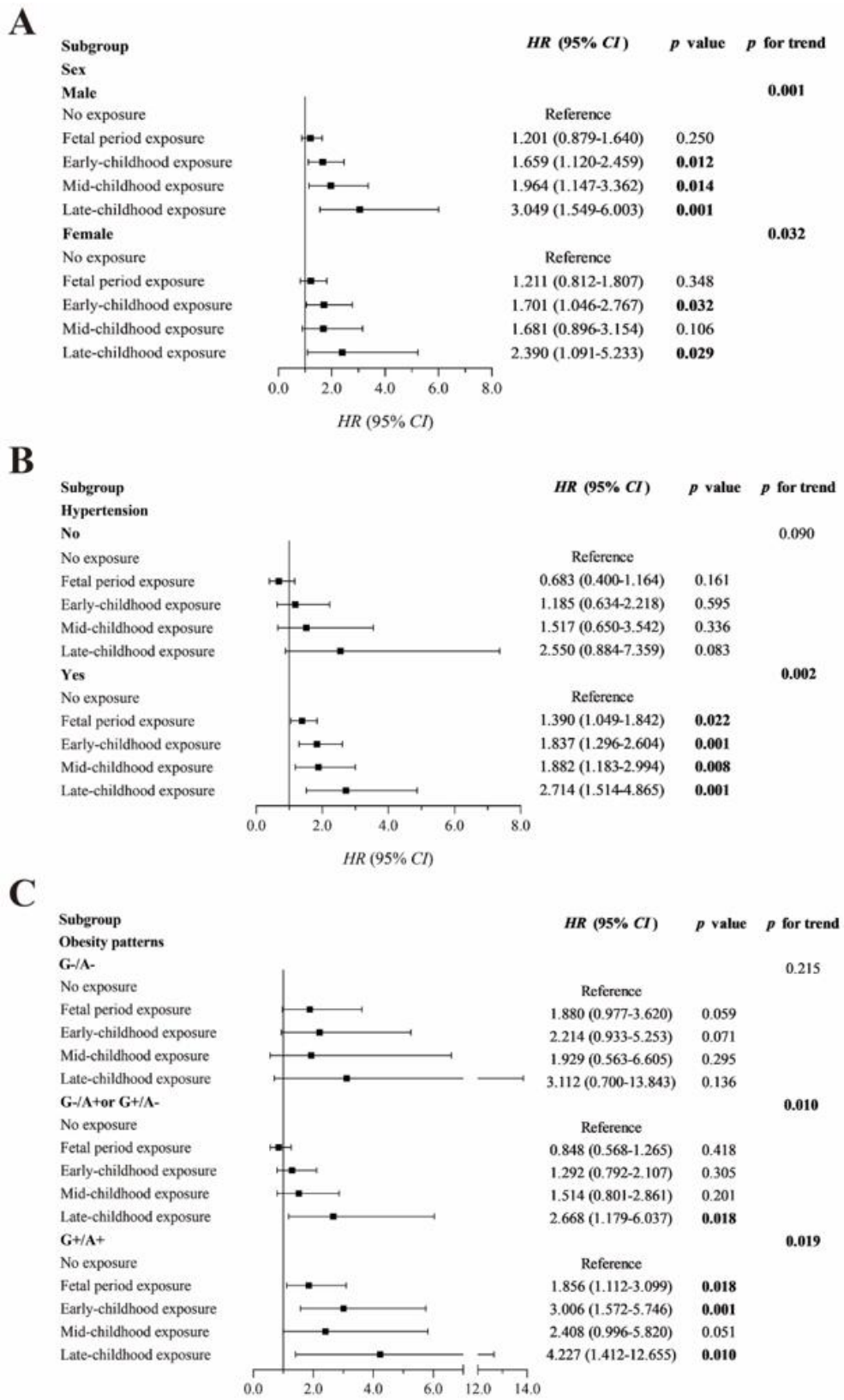

Figure 3. Forest plots of the associations between famine exposure and the incidence of DKD according to (a) sex (male = 1273, female = 1136), (b) hypertension (no = 642, yes = 1767), and (c) obesity patterns (G−/A− = 342, G+/A− or G−/A+ = 976, G+/ A+ = 473)
Note: All models adjusted for age, sex, BMI, smoking, drinking, hypertension, therapy methods, HbA1c, TG, and LDL-C; stratification variables were not adjusted in the corresponding analyses. Boldface indicates statistical significance (p <0.05).

Sensitivity analyses

When excluding participants born in 1958 and 1962, the results remained generally robust, despite a reduction in sample size (n = 2037, Supplementary Table 5). However, the association with DR and fetal famine exposure did not attain statistical significance, possibly due to the smaller sample size. After additional adjustment for diabetes duration, the results were generally consistent with the overall analysis (Supplementary Table 6).

DISCUSSION

In this retrospective cohort study of hospitalized T2D patients, we identified significant associations of famine exposure with the risk of DMC and its subtypes, including DR and DKD, but not DN. Childhood famine exposure was associated with a higher risk of incident overall DMC. Specifically, participants exposed to famine during fetal and childhood stages exhibited a higher risk of DR, particularly in those with hypertension. Similarly, famine exposure during childhood was linked to an increased risk of DKD, especially among individuals with hypertension or G+/A+ obesity patterns.

Prior studies have predominantly focused on the association between famine exposure in early life and specific DMC subtypes such as DR and CKD. For instance, research utilizing data from the Ukrainian National Diabetes Registry and the Hong Kong Diabetes Registry revealed a heightened risk of PDR in T2D patients exposed to perinatal famine during historical famines.[14] Additionally, investigations based on Great Chinese Famine suggested famine exposure during prenatal and childhood was associated with an increased CKD risk.[32-34] Furthermore, studies on the Dutch famine reported associations between famine exposure during mid-pregnancy and the prevalence of MUA in adulthood,[35] as well as an association between famine exposure during gestation and early postnatal life and proteinuria in adulthood among Chinese women.[36] Our study extends this body of research by providing evidence of the association between famine exposure in early life and the risk of overall DMC, thus filling a crucial gap in the literature. However, the results of this study were not fully consistent with the above studies. We found famine exposure in childhood appeared to have a greater impact than fetal life on the risk of DMC. Previous studies demonstrated that severe nutritional deficiencies or exposure to famine during childhood were associated with increased risks of chronic noncommunicable diseases in adulthood, including diabetes, CKD, cardiovascular disease, hypertension and metabolic syndrome.[34, 37, 38] These findings suggest that developmental plasticity in childhood may extend beyond the prenatal stage. Moreover, nutritional deficiencies during childhood have been shown to trigger persistent epigenetic changes, promoting structural and functional vascular alterations and inflammation in adulthood.[39, 40] Some studies showed that nutritional deficiencies during childhood had a detrimental effect on the function and morphology of microvascular systems in the retina and choroid,[41, 42] which may be indicative of the generalized systemic microvascular damage.[43] Furthermore, the differences in results also included the following explanations. On the one hand, these studies were limited to cross-sectional studies and could not evaluate the causal relationship between famine exposure and DMC. On the other hand, the diseases involved in these studies were not entirely consistent with ours, either only involving one classification or related diseases. Therefore, the discrepancy between this study and previous studies was reasonable.

Several potential mechanisms may underlie the association between famine exposure in early life with DMC in adulthood. Firstly, animal studies suggest that early-life malnutrition can negatively impact pancreatic function, leading to permanent metabolic disturbances in adulthood.[44, 45] Secondly, malnutrition during prenatal and early postnatal life may negatively influence microvascular expansion and remodeling, rendering vessels more susceptible to damage and dysfunction in response to elevated glucose levels later in life.[46] Thirdly, epigenetic modulation resulting from differential DNA methylations in adults who survived severe acute malnutrition during childhood may promote adverse metabolic phenotypes in adulthood.[47, 48]

Hypertension and obesity patterns emerged as modifiers of the associations of famine exposure with DMC. Significant interactions were observed between famine exposure and hypertension and obesity on DR and DKD. Consistent with the thrifty phenotype hypothesis, the occurrence of pathological changes following undernutrition in early life may be influenced by subsequent risk factors.[49] Notably, significant associations of famine exposure during fetal and childhood stages with a higher risk of DR and DKD in adulthood were predominantly observed in participants with hypertension. Similarly, previous research has demonstrated the beneficial effects of blood pressure control in reducing the risk of incident DMC,[50] possibly mediated through mechanisms such as oxidative stress and inflammation.[51] In addition, among participants with both general and abdominal obesity, famine exposure during fetal, early, and late childhood stages was associated with a higher risk of DKD in later life. Accumulating evidence have demonstrated that general and abdominal obesity are associated with increased risk of DKD in T2D patients.[52-54] Obesity might induce renal microvascular injury through mechanisms such as increasing renal tubular reabsorption and metabolic rate, increasing level of inflammatory mediators, releasing adipokines and so on.[55] These findings indicated that the key screening targets for DR and DKD were individuals who experienced undernutrition in early life with hypertension or both general and abdominal obesity, highlighting the importance of maintaining normal blood pressure, weight, and waist circumference in DMC prevention.

Strengths and limitations

Strengths of this study include its novelty as the first study of the longitudinal association between early-life famine exposure and overall DMC and its subtypes in adulthood. Exclusion of patients with a history of DMC enhanced the accuracy of event timing and minimized the potential for reverse causation. Additionally, anthropometric measurements provided more accurate assessments of obesity compared to self-reported data.

However, our study has several limitations. First, the classification of the Chinese famine was challenging due to its indefinite onset and conclusion, as well as variations in severity among different provinces. Misclassification of famine exposure was inevitable, and sensitivity analyses were conducted to address this issue. Second, the study participants comprised T2D patients hospitalized in Tianjin, potentially limiting generalizability to the broader Chinese population. Third, lack of data on physical activity, dietary intake, and family history of diseases. Limited our ability to adjust for these variables in the

analysis. Forth, the dates of participants' T2D first diagnosis in electronic medical records were based on patients recall rather than precise documentation, which may introduce bias in event timing analyses. Finally, the study is subject to left truncation, which possibly leading to underestimation of overall risk and dilution of the estimated exposure-outcome association.

Conclusions

In this study, famine exposure in early life was associated with higher risks of incident overall DMC, DR, and DKD. Particularly noteworthy was the association between famine exposure and DR, which was more pronounced in individuals with hypertension, while the association with DKD was heightened among those with hypertension or G+/A+ obesity patterns. Our findings provide additional evidence supporting the connection between early-life undernutrition and DMC. They offer valuable insights for identifying high-risk individuals and implementing targeted interventions to mitigate the risk of developing DMC in Chinese T2D patients.

ACKNOWLEDGEMENTS

We appreciate all of participants who enrolled in this study.

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

No AI-assisted technologies were used in the production of this study.

The authors reviewed and edited the content and takes full responsibility for the content of the publication.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare that they have no competing interests.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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