

# 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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Manuscript received 05 October 2025. Initial review completed 31 October 2025. Revision accepted 21 December 2025.

doi: 10.6133/apjcn.202604\_35(2).0006

**Supplementary Table 1.** Characteristics for included and excluded of individuals

Variables	Included individuals (n=2409)	Excluded individuals (n=7968)	p value
Age, median (P <sub>25</sub> , P <sub>75</sub> )	61.0 (58.0, 65.0)	61.0 (57.0, 65.0)	0.460
BMI, median (P <sub>25</sub> , P <sub>75</sub> ), kg/m <sup>2</sup>	25.8 (23.7, 28.2)	25.9 (23.7, 28.4)	0.656
Sex, n (%)			0.486
Male	1273 (52.8)	4275 (53.7)	
Female	1136 (47.2)	3693 (46.4)	
Smoking, n (%)			0.960
No	1401 (58.2)	1809 (58.2)	
Yes	1008 (41.8)	1298 (41.8)	
Drinking, n (%)			0.756
No	1558 (64.7)	1957 (64.3)	
Yes	851 (35.3)	1088 (35.7)	
Hypertension, n (%)			0.886
No	642 (26.7)	1275 (26.8)	
Yes	1767 (73.4)	3481 (73.2)	
Therapy methods, n (%)			0.166
Lifestyle intervention	144 (5.98)	330 (6.93)	
Oral medicine	805 (33.4)	1570 (33.0)	
Insulin	262 (10.9)	457 (9.60)	
Oral medicine and insulin	1198 (49.7)	2404 (50.5)	
TC, median (P <sub>25</sub> , P <sub>75</sub> ), mmol/L	4.94 (4.06, 5.81)	4.90 (4.11, 5.76)	0.800
TG, median (P <sub>25</sub> , P <sub>75</sub> ), mmol/L	1.51 (1.09, 2.13)	1.54 (1.08, 2.26)	0.195
HDL-C, median (P <sub>25</sub> , P <sub>75</sub> ), mmol/L	1.12 (0.95, 1.30)	1.11 (0.97, 1.29)	0.635
LDL-C, median (P <sub>25</sub> , P <sub>75</sub> ), mmol/L	3.30 (2.62, 3.97)	3.35 (2.63, 4.05)	0.114
HbA <sub>1c</sub> , median (P <sub>25</sub> , P <sub>75</sub> ), %	8.50 (7.40, 9.90)	8.60 (7.40, 9.90)	0.387

BMI, body mass index; HbA<sub>1c</sub>, haemoglobin A<sub>1c</sub>; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol.

Excluded individuals have missing data, sample size for each indicator: age (n = 7968), sex (n = 7968), BMI (n = 4426), smoking (n = 3107), drinking (n = 3045), hypertension (n = 4756), therapy methods (n = 4761), TC (n = 3894), TG (n = 3895), HDL-C (n = 3893), LDL-C, (n = 3895), HbA<sub>1c</sub> (n = 5514).

**Supplementary Table 2.** Odds ratio (OR) and 95% CI of the association of famine exposure with MAU (N=1359)

Famine exposure	Model 1	Model 2	Model 3
Fetal period exposure	1.465 (0.927-2.315)	1.489 (0.941-2.354)	1.574 (0.988-2.507)
Early-childhood exposure	2.706 (1.510-4.849)	2.690 (1.500-4.823)	3.025 (1.665-5.498)
Mid-childhood exposure	3.353 (1.524-7.376)	3.337 (1.516-7.345)	3.912 (1.744-8.776)
Late-childhood exposure	4.736 (1.723-13.018)	4.571 (1.662-12.574)	6.027 (2.133-17.036)
Trend test	1.489 (1.165-1.903)	1.475 (1.154-1.886)	1.574 (1.223-2.025)

BMI, body mass index; HbA<sub>1c</sub>, haemoglobin A<sub>1c</sub>; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; OR, odds 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, HbA<sub>1c</sub>, TG, and LDL-C were adjusted.

*p* <0.05 indicates statistical significance

**Supplementary Table 3.** The association between famine exposure and the incidence of DN by subgroups

Subgroup	n	No exposure	Fetal period exposure		Early-childhood exposure		Mid-childhood exposure	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Sex								
Male	1273	1.00 (reference)	0.824 (0.645-1.054)	0.123	0.806 (0.588-1.104)	0.179	0.676 (0.439-1.040)	0.075
Female	1136	1.00 (reference)	0.835 (0.638-1.093)	0.189	1.034 (0.740-1.443)	0.846	0.903 (0.584-1.397)	0.648
Hypertension								
No	642	1.00 (reference)	0.681 (0.483-0.961)	0.029	0.779 (0.512-1.187)	0.245	0.705 (0.398-1.247)	0.229
Yes	1767	1.00 (reference)	0.919 (0.741-1.140)	0.444	0.991 (0.757-1.298)	0.947	0.851 (0.594-1.220)	0.380
Obesity patterns								
G-/A-	342	1.00 (reference)	0.797 (0.488-1.302)	0.365	1.230 (0.664-2.278)	0.510	1.286 (0.549-3.013)	0.562
G-/A+ or	976	1.00 (reference)	0.731 (0.549-0.974)	0.032	0.747 (0.517-1.078)	0.119	0.586 (0.362-0.949)	0.030
G+/A-								
G+/A+	473	1.00 (reference)	1.552 (1.016-2.371)	0.042	2.252 (1.335-3.799)	0.002	2.386 (1.182-4.815)	0.015

  

Subgroup	Late-childhood exposure		p for trend	p for interaction
	HR (95% CI)	p value		
Sex				0.252
Male	0.609 (0.350-1.057)	0.078	0.089	
Female	1.282 (0.743-2.210)	0.372	0.355	
Hypertension				0.394
No	0.962 (0.471-1.963)	0.915	0.806	
Yes	0.959 (0.608-1.513)	0.857	0.800	
Obesity patterns				0.796
G-/A-	1.734 (0.624-4.814)	0.291	0.178	
G-/A+ or	0.717 (0.385-1.335)	0.294	0.208	
G+/A-				
G+/A+	4.145 (1.732-9.920)	0.001	0.003	

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.  $p < 0.05$  indicates statistical significance

**Supplementary Table 4.** The association between famine exposure and the incidence of DMC by subgroups

Subgroup	n	No exposure	Fetal period exposure		Early-childhood exposure		Mid-childhood exposure	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Sex								
Male	1273	1.00 (reference)	1.040 (0.850-1.274)	0.702	1.223 (0.947-1.579)	0.124	1.201 (0.847-1.703)	0.305
Female	1136	1.00 (reference)	1.026 (0.823-1.280)	0.817	1.294 (0.984-1.703)	0.066	1.355 (0.948-1.937)	0.096
Hypertension								
No	642	1.00 (reference)	0.868 (0.653-1.155)	0.333	1.064 (0.746-1.515)	0.733	1.241 (0.773-1.994)	0.371
Yes	1767	1.00 (reference)	1.108 (0.929-1.322)	0.253	1.357 (1.090-1.689)	0.006	1.301 (0.971-1.743)	0.078
Obesity patterns								
G-/A-	342	1.00 (reference)	0.959 (0.648-1.419)	0.833	1.146 (0.690-1.903)	0.598	1.149 (0.567-2.327)	0.700
G-/A+ or	976	1.00 (reference)	0.901 (0.711-1.142)	0.389	1.137 (0.845-1.530)	0.398	1.176 (0.798-1.733)	0.412
G+/A-								
G+/A+	473	1.00 (reference)	1.530 (1.081-2.165)	0.016	2.196 (1.434-3.362)	<0.001	2.079 (1.168-3.699)	0.013

  

Subgroup	Late-childhood exposure		p for trend	p for interaction
	HR (95% CI)	p value		
Sex				0.785
Male	1.403 (0.900-2.186)	0.135	0.124	
Female	1.830 (1.169-2.863)	0.008	0.006	
Hypertension				0.280
No	1.701 (0.937-3.086)	0.081	0.076	
Yes	1.648 (1.140-2.382)	0.008	0.009	
Obesity patterns				0.461
G-/A-	1.434 (0.612-3.364)	0.407	0.370	
G-/A+ or	1.482 (0.897-2.446)	0.124	0.077	
G+/A-				
G+/A+	3.601 (1.761-7.364)	<0.001	0.001	

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.  $p < 0.05$  indicates statistical significance

**Supplementary Table 5.** The association of famine exposure with the incidence risk of DMC with removing participants born in 1958 and 1962 (N=2037)

	Model 1		Model 2		Model 3	
	<i>HR (95% CI)</i>	<i>p value</i>	<i>HR (95% CI)</i>	<i>p value</i>	<i>HR (95% CI)</i>	<i>p value</i>
Overall DMC						
Fetal period exposure	1.031 (0.873-1.218)	0.720	1.032 (0.873-1.220)	0.709	1.056 (0.891-1.250)	0.530
Early-childhood exposure	1.260 (1.001-1.586)	0.049	1.253 (0.994-1.578)	0.056	1.267 (1.004-1.597)	0.046
Mid-childhood exposure	1.391 (1.053-1.838)	0.020	1.388 (1.051-1.834)	0.021	1.327 (1.001-1.760)	0.050
Late-childhood exposure	1.847 (1.299-2.628)	0.001	1.846 (1.297-2.627)	0.001	1.682 (1.179-2.399)	0.004
Trend test	1.176 (1.082-1.278)	<0.001	1.175 (1.081-1.277)	<0.001	1.140 (1.048-1.240)	0.002
DR						
Fetal period exposure	1.163 (0.970-1.393)	0.102	1.166 (0.973-1.397)	0.097	1.194 (0.994-1.434)	0.058
Early-childhood exposure	1.500 (1.169-1.924)	0.001	1.493 (1.164-1.916)	0.002	1.521 (1.184-1.954)	0.001
Mid-childhood exposure	1.694 (1.254-2.290)	0.001	1.693 (1.253-2.289)	0.001	1.635 (1.204-2.219)	0.002
Late-childhood exposure	2.196 (1.500-3.217)	<0.001	2.195 (1.498-3.217)	<0.001	2.010 (1.367-2.953)	<0.001
Trend test	1.216 (1.111-1.330)	<0.001	1.215 (1.110-1.330)	<0.001	1.180 (1.078-1.293)	<0.001
DKD						
Fetal period exposure	1.171 (0.890-1.540)	0.260	1.187 (0.901-1.563)	0.223	1.249 (0.943-1.655)	0.121
Early-childhood exposure	1.661 (1.144-2.414)	0.008	1.658 (1.140-2.413)	0.008	1.757 (1.202-2.568)	0.004
Mid-childhood exposure	1.879 (1.196-2.953)	0.006	1.885 (1.198-2.966)	0.006	1.925 (1.210-3.061)	0.006
Late-childhood exposure	2.763 (1.562-4.888)	<0.001	2.731 (1.542-4.838)	0.001	2.837 (1.584-5.080)	<0.001
Trend test	1.288 (1.126-1.474)	<0.001	1.282 (1.121-1.467)	<0.001	1.281 (1.118-1.469)	<0.001
DN						
Fetal period exposure	0.858 (0.699-1.053)	0.143	0.859 (0.700-1.055)	0.148	0.881 (0.716-1.084)	0.230
Early-childhood exposure	0.894 (0.672-1.188)	0.440	0.891 (0.670-1.185)	0.427	0.904 (0.679-1.204)	0.489
Mid-childhood exposure	0.872 (0.618-1.230)	0.434	0.871 (0.617-1.229)	0.432	0.852 (0.601-1.208)	0.369
Late-childhood exposure	1.047 (0.677-1.620)	0.836	1.047 (0.677-1.621)	0.836	0.991 (0.638-1.538)	0.967
Trend test	1.026 (0.925-1.137)	0.630	1.025 (0.925-1.137)	0.635	1.006 (0.906-1.116)	0.913

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, HbA<sub>1c</sub>, TG, and LDL-C were adjusted

*p* <0.05 indicates statistical significance

**Supplementary Table 6.** The longitudinal association of famine exposure with the incidence of DMC (adjusting disease duration)

	<i>HR</i>	95% <i>CI</i>	<i>p</i> value
Overall DMC			
Fetal period exposure	1.076	0.928 - 1.248	0.330
Early-childhood exposure	1.291	1.076 - 1.548	0.006
Mid-childhood exposure	1.391	1.092 - 1.771	0.008
Late-childhood exposure	1.603	1.181 - 2.175	0.002
Trend test	1.130	1.051 - 1.216	0.001
DR			
Fetal period exposure	1.238	1.054 - 1.454	0.009
Early-childhood exposure	1.555	1.277 - 1.893	<0.001
Mid-childhood exposure	1.742	1.340 - 2.265	<0.001
Late-childhood exposure	1.914	1.374 - 2.666	<0.001
Trend test	1.183	1.093 - 1.281	<0.001
DKD			
Fetal period exposure	1.194	0.936 - 1.523	0.153
Early-childhood exposure	1.581	1.175 - 2.127	0.002
Mid-childhood exposure	1.837	1.239 - 2.723	0.002
Late-childhood exposure	2.449	1.489 - 4.029	<0.001
Trend test	1.251	1.110 - 1.409	<0.001
DN			
Fetal period exposure	0.873	0.729 - 1.045	0.138
Early-childhood exposure	0.947	0.759 - 1.183	0.631
Mid-childhood exposure	0.864	0.642 - 1.162	0.332
Late-childhood exposure	0.924	0.635 - 1.345	0.679
Trend test	0.986	0.901 - 1.079	0.760

DMC, diabetic microvascular complications; DR, diabetic retinopathy; DKD, diabetic kidney disease; DN, diabetic neuropathy; BMI, body mass index; HbA<sub>1c</sub>, haemoglobin A<sub>1c</sub>; TG, triacylglycerol, LDL-C, low-density lipoprotein cholesterol; *CI*, confidence interval; *HR*, hazard ratio.

Age, sex, BMI, smoking, drinking, hypertension, therapy methods, HbA<sub>1c</sub>, TG, LDL-C and disease duration were adjusted. *p* <0.05 indicates statistical significance