Association between fetal famine exposure and risk of type 2 diabetes: a prospective cohort study

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Title page

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1 **ABSTRACT**

2 To explore the effects of fetal experience of famine on the onset of type 2 diabetes mellitus (T2DM) in adults.

3 The analysis included 16,594 participants of the Kailuan Study, who were free of diabetes at baseline (2006).

4 According to the date of birth, the individuals born on 1 October 1962-30 September 1964 were divided into the

5 non-exposed group (used as the reference group) , the individuals born on 1 October 1959-30 September 1961

6 were divided into the fetal exposure group, and the early childhood exposure group included those born on 1

7 October 1956-30 September 1958. The cumulative incidence of T2DM for each group was calculated and

8 compared among three groups, and the cox regression model was used to analyze the effects of fetal experience

9 of famine on risk of diabetes. During a median 10.27 years (170,358 person-years) of follow-up (2006-2017),

10 3,509 incident T2DM cases were identified, and the cumulative incidence rate was 19.46%. The cumulative

11 incidences of T2DM in non-exposed group, fetal exposure group and early childhood exposure group were

12 17.38%, 20.85% and 20.65% (P<0.01). After adjusting for confounding factors, the hazard ratio (HR) of T2DM

13 in fetal exposure group was 1.222(95% CI: 1.087-1.374, P<0.01), compared with the reference group. The

14 association was modified by gender and hypertension (both P interaction less than 0.05). Fetal famine exposure

15 may increase the risk of T2DM in adults. This association was more pronounced among female and

16 hypertensives.

17

18 Novelty:

- 19 • The association was modified by gender and hypertension
- 20 • Long follow-up time

21

22 **Key words:** Famine, diabetes mellitus, cohort, incidence

Introduction

Diabetes mellitus (DM) is a global major public health problem (Zimmet et al. 2018), complications involving multiple organs (e.g., kidney, brain, eye), with high disability and mortality (Velmurugan et al. 2017). In recent years, the incidence and prevalence of DM have continued to rise globally (Chatterjee et al. 2017). The International Diabetes Federation (IDF) estimated that the global prevalence of diabetes (20-79 years) will reach 9.9% in 2045. However, in China, the prevalence has reached 10.9% in 2017 (Cho et al. 2018). In addition, according to WHO prediction, the number of deaths from DM will double during the period 2005-2030. However, as a complex metabolic disease with multiple risk factors, the exact cause of DM remains to be unclearly. Exploring the new risk factors would be helpful in prevention of DM.

The “Developmental Origins of Health and Disease” hypothesis suggests that unfavorable factors in early development, especially intrauterine nutrition imbalance, will affect the health of later life (Burlina et al. 2019; Gowland et al. 2015). Dutch (Lumey et al. 2009; Lumey et al. 2011; Ravelli et al. 1998) and Ukrainian (Lumey et al. 2015; Vaiserman et al. 2009) famine studies have suggested that exposure to famine during pregnancy can increase the risk of diabetes in adulthood, but Stanner et al. (Stanner et al. 1997) used data from the Leningrad defending war between 1941 and 1944 and found no correlation. Another study showed that only the coexistence of prenatal malnutrition and abdominal obesity was associated with a higher risk of diabetes, while famine alone was not associated with a higher risk of diabetes (Meng et al. 2018). In brief, inconsistent findings have been reported on the association between fetal famine exposure and the risk of diabetes. It is still not clear whether fetal exposure to famine is associated with an increased risk of DM in adulthood.

44 The Great Famine of China (1959-1961) was one of the greatest famines in human history. During this period,
45 the population was in a state of malnutrition for a long time, causing millions of extra deaths in China (Wang et
46 al. 2016). Up to date, the individuals who experienced fetal famine exposure has grown up to the age of
47 susceptible for DM. The aim of this study was to investigate whether fetal exposure to the Chinese famine is
48 associated with an increased risk of diabetes.

49

50 **Methods**

51 **Study population**

52 The Kailuan study is a prospective cohort study enrolled many employees at Kailuan Community. In 2006, all
53 155,418 residents aged 18 or over were invited to participate. A total of 101,510 participants (18-98 years old,
54 20,400 women and 81,110 men) agreed to participate in and completed the baseline survey in the period from
55 2006 to 2007 (2006 survey, baseline of this study) (Wang et al. 2015). There were no demographic differences
56 between study participants and non-participants, except for a small difference in sex (79.9% of males
57 participated versus 85.9% males in the Kailuan community). All participants responded to questionnaire, took
58 physical examinations and laboratory tests biennially.

59

60 In the current study, we restricted the analysis to participants who were born between 1 October 1956 and 30
61 September 1964 (n=22,802). The exact dates of the start and the end of the Chinese famine were not available
62 and not the same across regions. To minimize the impact of misclassified exposure time on the relationship
63 between fetal exposure to famine and diabetes risk, we excluded those born between 1 October 1958 and 30
64 September 1959 (n=2,679) or between 1 October 1961 and 30 September 1962 (n=2,088). In addition, 1441

participants with DM prior to 2006 and one individual with incomplete data were excluded from 2006 survey, 16,594 participants (4,350 women and 12,244 men, mean age =46.42 years) were included in the analysis. This study protocol was in accordance with the guidelines of the Helsinki Declaration, and was approved by the Ethics Committee of the Kailuan Medical Group, Kailuan Company. All participants provided their written informed consent.

Assessment of famine exposure

All participants reported their date of birth at baseline. Consistent with previous Chinese famine studies (Wang et al. 2016; Wang et al. 2016), the date of birth was the basis for the classification of famine exposure. People born between 1 October 1959 and 30 September 1961 were classified as fetal famine exposure groups (45-47 years old in 2006), and those born between 1 October 1956 and 30 September 1958 were classified as early childhood famine exposure groups and a non-exposed group (born between 1 October 1962 to 30 September 1964).

Follow up and T2DM events

This study began in 2006 and was followed up regularly every two years until 31 December 2017. The content of the follow-up is consistent with the baseline survey, including physical examinations and laboratory tests. According to the guidelines of the American Diabetes Association, participants were determined to have diabetes if they were currently treated with insulin or oral hypoglycemic drugs, or if fasting blood glucose (FBG) levels were not less than 7.0 mmol/L in any of the 2008, 2010, 2012, 2014 and 2016 surveys (Wang et al. 2015).

86

87 **Assessment of covariates**

88 Information on age, sex, smoking, drinking, physical activity, education level, income level and previous
89 disease history (such as diabetes) and family history of diabetes were collected on a self-reported questionnaire.
90 As previously mentioned (Zhang et al. 2013), height, weight and blood pressure were assessed by trained nurses
91 during the survey; body mass index was calculated as body weight (kg) / height (m) ².

92

93 After fasting for at least 12 hours, blood samples were collected on the morning of the survey and injected into
94 a vacuum tube containing Ethylene Diamine Tetra Acetic acid (EDTA). Plasma glucose, total cholesterol,
95 triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C),
96 creatinine and hypersensitive C-reactive protein were measured by automatic analyzer (Hitachi 747; Hitachi,
97 Tokyo, Japan) in the central laboratory of Kailuan General Hospital.

98

99 **Statistical Analysis**

100 All data were entered by Oracle10.2g database, and exported as DBF format file. All data were applied by SAS
101 9.4 (SAS Institute, Inc., Cary, North Carolina).

102

103 The measurement data were expressed as ($\bar{x}\pm s$), and analysis of variance were used to test differences in
104 continuous variables. The counting data were expressed by percentage n (%), and the χ^2 test was used to
105 compare among groups. P<0.05 (two-side test) showed that the difference was statistically significant.
106 Participants contributed person-years from the date at baseline to the diagnosis of diabetes, death, loss to follow

up or 31 December 2017, whichever came first. A Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) to analyze the impact of fetal experience of famine on the risk of T2DM.

The multivariable model was adjusted for potential confounders, including sex (for whole cohort only), education (no attending school or primary school, middle school or high school, college degree or higher), body mass index (≥ 30.0 , 25.0 - 29.9 , or < 25.0 kg/m²), systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C, LDL-C, income level ($< ¥600$, $¥600$ - 1000 , or $\geq ¥1000$), smoking (yes/no), drinking (yes/no), physical activity (yes/no), family history of diabetes (yes/no), use of antihypertensive, and lipid-lowering medications (yes/no for each). We used the non-exposed group (born on 1 October 1962-30 September 1964) as reference group. The proportional-hazards assumption was satisfied. To explore whether the association between fetal exposure to famine and T2DM risk was modified by sex, overweight or hypertension in later life, we tested the multiplicative interaction by comparing the -2log likelihood.

Sensitivity analysis: To eliminate the influence of medication history on diabetes risk, individuals who took antihypertensive medications or lipid-lowering medications were deleted respectively, and the above statistical analysis was repeated.

Results

In the current study, 16,594 participants were finally included in the statistical analysis, 12,244 (73.79%) males and 4,350 (26.21%) females. There were 6,365 individuals in the non-exposed group, 3,582 individuals in the

fetal exposure group, and 6,647 individuals in the early childhood exposure group. The body mass index and triglyceride of the fetal exposure group were higher than those of other groups, and the low density lipoprotein cholesterol was lower than those of other two groups (Table 1). The blood glucose levels of the three groups were increasing year by year. Until the end of 2017, the blood glucose level of the fetal exposure group slightly exceeded that of the early childhood exposure group (Figure 1).

During the follow-up period of 10.27 years (170,358 person-years), a total of 3,509 cases of T2DM were diagnosed, with a cumulative incidence rate of 19.46%. The 10-year cumulative incidence rate obtained in this study was 20.85% in the fetal exposure group, 20.65% in the early childhood exposure group and 17.38% in the non-exposed group (Figure 2). As expected, the group of the fetal exposure had the highest T2DM incidence. After log-rank test, the cumulative incidence of diabetes in different groups was statistically significant (Figure 2). The results were similar for both men and women.

In the multivariable-adjusted analysis, participants exposed to famine in fetal period showed an increased risk of developing diabetes (HR:1.222, 95%CI 1.087,1.374) than those in reference group (Table 2). The risk of diabetes in participants exposed to famine in fetal period was even higher than that in participants exposed to famine in early childhood (~3 years older than fetal exposure group). In order to eliminate the confounding effects of medications, we excluded individuals taking antihypertensive medications, lipid-lowering medications, or both in the sensitivity analysis. Similarly, the fetal famine exposure group had the highest risk (Table 2).

The relationship between fetal exposure to famine and diabetes risk seems to be altered by gender or hypertension (Table 3). The association were more connected in female or individuals with hypertension (both P interactions were <0.05). On the contrary, we did not observe a significant interaction between famine exposure and overweight status (Table 3). In addition, we have performed a sensitivity analysis for all those persons. And we still observe a significant association between exposure to famine and a higher risk of DM (Table 4).

Discussion

Principal findings and implications

In this study, fetal exposure to the Chinese famine was associated with an increased risk of T2DM in later years. And the association was more pronounced in female or hypertension patients. Based on the latest edition of "World Food Security and Nutrition" (FAO 2020), 690 million people have suffered from hunger in 2019. The United Nations reported that the COVID-19 epidemic may increase the number of chronically hungry by more than 130 million people worldwide by the end of 2020 (a sudden severe hunger during the epidemic may further increase this number), which means that nearly a billion people will suffer from malnutrition (FAO 2020). Therefore, our findings are helpful in identifying individuals with high-risk of T2DM and implementing accurate prevention in poor or disaster areas.

Comparisons with other studies

Previous cross-sectional studies have shown that famine exposure was associated with high prevalence of T2DM in adulthood (Li et al. 2011; Li et al. 2014; Xu et al. 2016), which were consistent with our prospective

cohort study. Another study showed that coexistence of prenatal experience of undernutrition and abdominal obesity, not prenatal experience of undernutrition, was associated with a higher risk of diabetes (Meng et al. 2018). As is known, the severity of the Great Famine in China varies from region to region, and there is a lack of formal literature on the severity of famine in China's sub-provincial regions. In their study, the participants enrolled both from the southwest and the northeast, however, our participants is relatively concentrated. This might be the possible reason for the different results. In addition, obesity and type 2 diabetes mellitus (T2DM) are public health issues that are growing worldwide, and their incidence rates are closely correlated (World Health Organization. 2016). Abdominal obesity is a risk factor for T2DM and the hypothetical underlying mechanisms are an abnormal adipokine profile and increased insulin resistance (Lim et al. 2013). Another reason for the different results may be the abdominal obesity plays a role.

Li et al. (Li et al. 2017) suggested that uncontrolled age differences between famine births and control births could explain most effects commonly attributed to the famine. Famine effects were not present in patients with T2DM when they combined famine birth with prenatal famine and postnatal famine as a single control group to control age effects in the meta-analysis (OR = 0.96; 95% CI: 0.73-1.28) (Li et al. 2017). In this study, we still observed an increased risk of T2DM in fetal-exposed participants (HR=1.019, 95%CI 1.002-1.048), relative to early child exposed participants, which were -3 years older.

Potential mechanisms and explanations

Possible causal relationship between fetal exposure to famine and T2DM. The possible mechanisms are as follows: First, embryonic famine exposure may cause pancreatic developmental disorders, β -cell dysfunction

and insulin deficiency (Green et al. 2010). Dutch famine shows that people exposed to famine in early pregnancy have lower glucose tolerance during adulthood, and those exposed to famine during the second trimester have insufficient levels of insulin release and insulin resistance (de Rooij et al. 2006). Second, when the embryonic period experienced famine, the growth and development of the body will adapt to the poor nutrient environment (Nielsen et al. 2014). When the acquired environment does not match the embryonic environment, the body will have dysfunction or damage (Thorn et al. 2011). Third, malnutrition during embryonic development alters the level of epigenetic modification of genes, such as changes in the level of IGF2 gene methylation in populations exposed to Dutch famine (Heijmans et al. 2008) and these epigenetic changes affect islet beta cell function (Gluckman et al. 2008). In addition, exposure to malnutrition during the embryonic period can also affect appetite and fat storage in adulthood, showing a preference for eating high-fat foods rather than exercise (Langley-Evans et al. 2005; Lukaszewski et al. 2013).

In addition, we observed that the association between fetal exposure to famine and T2DM risk could be modified by gender. Studies have shown that the relationship between women's early experience of famine and poor health is more closely related than men's (Wang et al. 2017; Yang et al. 2008) which is exactly the same to our findings. Several possible mechanisms can explain this gender difference. Studies have shown that exposure to famine during pregnancy may result in a constant change in the level of DNA methylation of multiple imprinted and non-imprinted genes with different biological functions (Tobi et al. 2009), and the adaptation of male and female fetuses to developmental challenges; Dutch famine showed that poor prenatal conditions trigger a constant change in DNA methylation, and these changes vary by gender (Tobi et al. 2009). Furthermore, the interaction between sex hormones and DNA methyltransferase expression may be a factor

(Yamagata et al. 2009).

213

The association also was more pronounce in hypertensive participants. Some studies believed that hypertension (a core component) based on metabolic syndrome (insulin resistance is the core of MS) is an indicator that is conducive to identifying insulin resistance (Wang et al. 2017; Pravenec et al. 2008). It has been confirmed that high blood pressure is closely related to the risk of diabetes (Strain et al. 2018; Tesfaye et al. 2019). In addition, studies have pointed out that famine is related to insulin resistance (Li et al. 2011; Li et al. 2014; Xu et al. 2016). Therefore, the mechanism that famine and high blood pressure together lead to insulin resistance can explain the mutual effect of both on the onset of diabetes.

221 **Limitations and Strengths**

This study included several advantages, including large sample size, long follow-up time (once every two years, more accurate person-year) and reasonable control for potential confounding factors. The prospective design, with the exclusion of prevalent cases of diabetes at baseline, could prevent incidence-prevalence bias and minimize the possibility of reverse causation for human body function measurement measures, lifestyle covariates and diabetes. However, some limitations also exist. First, we could not find a control group with similar age as the fetal-exposed group. Because the Chinese famine swept across all areas in China, it was difficult to find people who did not suffer from famine. We still observed an increased risk of DM in fetal-exposed participants, relative to early child exposed participants which were -3 years older. Secondly, all participants were recruited from the Kailuan community, and most of the participants were male (79.9%). Therefore, the observed results may not be promoted. In addition, there is no clear start and end date for the Great Famine in China, there may be misclassification of exposure, and the famine effect may be diluted. In

order to minimize the effects of misclassified exposure time on the relationship between prenatal exposure to famine and diabetes risk, we excluded those born on 1 October 1958 to 30 September 1959 and 1 October 1961 to 30 September 1962, and still observed the association.

Conclusion

In conclusion, fetal exposure to famine is associated with the risk of developing T2DM in the middle and late years. Our study provided evidence to the prevention across the lifespan, from fetal to later life, to mitigate diabetes risk in Chinese. A large sample of women and an age-comparable reference group need to be further studied to confirm our results.

Article Information

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Author Contributions

WANG C contributed to the design of the study, collected and analyzed data, contributed to the discussion, and drafted the manuscript. LUO XY, Tao BN and DU W collected data, contributed to the discussion. HOU LY, CHEN SH, and YANG P researched data, contributed to discussion. LI Y and WU SL conceptualized and designed the study, interpreted the data and critically revised the manuscript for the intellectual content.

Conflict of interest disclosure

We declare that we have no conflict of financial and commercial interest.

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Data and Resource Availability

Deidentified data are available to researchers on request by contacting with Dr. LI or Dr. WU.

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Figure captions:

Figure 1 Trends in blood glucose levels in three groups
Figure 2 Cumulative incidence curve of DM in three group
 (log-rank $P < 0.004$)

Table 1 Baseline characteristics of 16,594 Kailuan participants according to famine exposure

	Non exposed	Famine exposure		p
		Fetal exposure	Early childhood exposure	
		1 October 1959 to 30 September 1961	1 October 1956 to 30 September 1958	
		1964(n=6365, Ref.)	1961(n=3582)	
Age (year)	43.37±0.62	46.46±0.57	49.32±0.63	<0.001
Men (%)	4555(71.56)	2518(70.30)	5171(77.79)	<0.001
BMI (kg/m ²)	25.02±3.40	24.86±3.33	25.02±3.27	0.035
WHR				<0.001
M≥0.9, W≥0.85	3135(49.25)	1832(51.14)	3465(52.13)	
M<0.9, W<0.85	3230(50.75)	1750(48.86)	3182(47.87)	
SBP (mmHg)	125.58±18.70	126.59±19.07	128.96±19.60	<0.001
DBP (mmHg)	83.11±12.19	83.16±11.95	83.97±11.88	<0.001
TC (mmol/L)	4.90±1.10	4.96±1.05	4.99±1.10	<0.001
TG (mmol/L)	1.73±1.47	1.63±1.32	1.67±1.40	0.069
HDL-C (mmol/L)	1.53±0.37	1.53±0.37	1.54±0.38	0.376

LDL-C (mmol/L)	2.34±0.81	2.36±0.80	2.34±0.89	0.477
Smoker (%)	2432(38.53)	1383(39.00)	2808(42.88)	<0.001
Drinker (%)	2608(41.28)	1402(39.53)	2713(41.46)	<0.001
Active exercise (%)	372(5.94)	233(6.61)	577(8.84)	<0.001
Income level (%)				0.388
Low	1909(30.45)	1100(31.20)	2009(30.78)	
Medium	4005(63.89)	2253(63.90)	4193(64.23)	
High	355(5.66)	173(4.91)	326(4.99)	
Education (%)				<0.001
Low	166(2.65)	116(3.29)	306(4.68)	
Medium	5675(90.54)	3278(93.02)	6022(92.18)	
High	427(6.81)	130(3.69)	205(3.14)	
Family history of diabetes (%)	383(6.02)	194(5.42)	307(4.62)	<0.001
Hypertension (%)	2225(34.96)	1259(35.15)	2669(40.15)	<0.001
FBG (mmol/L)	5.08±0.65	5.11±0.67	5.13±0.69	<0.001
Use of antihypertensive medications (%)	344(5.40)	211(5.89)	545(8.20)	<0.001

Use of lipid-lowering medications (%)	27(0.42)	14(0.39)	25(0.38)	0.907
Hyperlipidemia (%)	2160(33.94)	1118(31.21)	2285(34.38)	0.004

Continuous variables are presented as mean ± SD; Categorical variables are presented as numbers or percentages.

Income level: Low income of less than ¥600 per month, Medium income of ¥600-1000 per month, High income of more than ¥1,000 per month.

Education: Not attending school or elementary school for low education, Junior high school or high school for moderate education, College degree or above is higher education.

Abbreviations: BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBP, Fasting blood glucose.

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Table 2 Adjusted hazard ratio and 95% confidence interval for incidence of diabetes mellitus in the total population and sensitivity analysis

	Non exposed	Famine exposure	
		Fetal exposure	Early childhood exposure
	1 October 1962 to 30 September 196(n=6365, Ref.)	1 October 1959 to 30 September 1961(n=3582)	1 October 1956 to 30 September 1958(n=6647)
Total			
# of case / participants	727/6365	481/3582	861/6647
Incidence (/1000 person years)	11.0	13.1	12.7
Model 1	1	1.187(1.057,1.331)	1.147(1.039,1.266)
Model 2	1	1.240(1.104,1.394)	1.137(1.028,1.257)
Model 3 ^a	1	1.222(1.087,1.374)	1.120(1.011,1.240)
Sensitivity analysis			
Excluding 1100 participants with antihypertensive medications			
# of case / participants	665/6021	447/3371	755/6102
Incidence (/1000 person years)	10.7	13.0	12.1
Model 1	1	1.214(1.077,1.369)	1.132(1.020,1.256)
Model 2	1	1.268(1.124,1.432)	1.129(1.015,1.255)
Model 3 ^b	1	1.249(1.105,1.411)	1.107(0.994,1.232)
Excluding 66 participants with lipid-lowering medications			

# of case / participants	723/6338	478/3568	858/6622
Incidence (/1000 person years)	11.0	13.1	12.7
Model 1	1	1.185(1.056,1.330)	1.149(1.041,1.269)
Model 2	1	1.237(1.100,1.390)	1.138(1.029,1.259)
Model 3 ^c	1	1.219(1.083,1.371)	1.121(1.012,1.241)
Excluding 1129 participants with both above medications			
# of case / participants	665/6011	445/3363	753/6091
Incidence (/1000 person years)	10.7	12.9	12.1
Model 1	1	1.209(1.072,1.363)	1.129(1.017,1.253)
Model 2	1	1.262(1.118,1.425)	1.125(1.012,1.251)
Model 3 ^d	1	1.243(1.100,1.405)	1.103(0.991,1.228)

HR indicates hazard ratio;

Model 1: unadjusted.

Model 2: multivariate adjustment was made for sex, body mass index (≥ 30.0 kg/m², 25.0-29.9 kg/m², or < 25.0 kg/m²), systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C, LDL-C, family history of diabetes (yes/no).

Model 3^a: on the basis of model 2, smoking (yes/no), alcohol consumption (yes/no), physical activity(yes/no), education (no attending school or primary school, middle school or high school, college degree or higher), income level ($< ¥600$, ¥600-1000, or $\geq ¥1000$), use of antihypertensive (yes/no for each) and lipid-lowering medications (yes/no for each) were further adjusted in the whole population.

Model 3^b: Adjusted for all variables in model 3^a except the use of antihypertensive medications.

Model 3^c: Adjusted for all variables in model 3^a except the use of lipid-lowering medications.

Model 3^d: Adjusted for all variables in model 3^a except the use of antihypertensive and lipid-lowering medications.

Table 3 Adjusted hazard ratio and 95% confidence interval for incidence of diabetes mellitus, by famine exposure, and by sex, body mass index, blood pressure

	Non exposed	Famine exposure		P (interaction)
		Fetal exposure	Early childhood exposure	
	1 October 1962 to 30 September 1964 (n=6365, Ref.)	1 October 1959 to 30 September 1961(n=3582)	1 October 1956 to 30 September 1958(n=6647)	
	HR (95%CI)	HR (95%CI)	HR (95%CI)	
Male				0.02
# of case / participants	600/4555	365/2518	688/5171	
Incidence (/1000 person years)	12.8	14.3	13.0	
Multivariate-adjusted hazard ratio ¹	1	1.173(1.027,1.339)	1.057(0.944,1.183)	
Female				
# of case / participants	127/1810	116/1064	173/1476	
Incidence (/1000 person years)	6.7	10.5	11.4	
Multivariate-adjusted hazard ratio ¹	1	1.429(1.105,1.849)	1.418(1.113,1.805)	
Overweight^a				0.91
# of case / participants	473/3006	302/1635	575/3149	
Incidence (/1000 person years)	15.6	18.6	18.4	
Multivariate-adjusted hazard ratio ²	1	1.208(1.042,1.400)	1.179(1.041,1.337)	
Non-overweight				
# of case / participants	254/3359	179/1947	286/3498	

Incidence (/1000 person years)	7.2	8.8	7.8
Multivariate-adjusted hazard ratio ²	1	1.231(1.013,1.494)	0.999(0.839,1.191)
Hypertension^b			0.04
# of case / participants	359/2225	230/1259	472/2669
Incidence (/1000 person years)	16.0	18.3	17.7
Multivariate-adjusted hazard ratio ³	1	1.211(1.023,1.433)	1.156(1.003,1.332)
Non-hypertension			
# of case / participants	368/4140	251/2323	389/3978
Incidence (/1000 person years)	8.5	10.4	9.4
Multivariate-adjusted hazard ratio ³	1	1.231(1.044,1.451)	1.070(0.924,1.240)

HR indicates hazard ratio;

a Overweight was defined as body mass index ≥ 25 kg/m².

^b Hypertension was defined as a systolic equal or higher than 140mmHg or a diastolic blood pressure equal or higher than 90mmHg or use antihypertensive agents.

¹ Adjusted for body mass index (≥ 30.0 kg/m², 25.0-29.9 kg/m², or < 25.0 kg/m²), systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C, LDL-C, Family history of diabetes (yes/no). smoking (yes/no), alcohol consumption (yes/no), physical activity(yes/no), education (no attending school or primary school, middle school or high school, college degree or higher), income level ($< \text{¥}600$, $\text{¥}600\text{-}1000$, or $\geq \text{¥}1000$), use of antihypertensive (yes/no for each) and lipid-lowering medications (yes/no for each).

² Adjusted for sex, systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C, LDL-C, Family history of diabetes (yes/no). smoking (yes/no), alcohol consumption (yes/no), physical activity(yes/no), education (no attending school or primary school, middle school or high school, college degree or higher), income level ($< \text{¥}600$, $\text{¥}600\text{-}1000$, or $\geq \text{¥}1000$), use of antihypertensive (yes/no for each) and lipid-lowering medications (yes/no for each).

³ Adjusted for sex, body mass index (≥ 30.0 kg/m², 25.0-29.9 kg/m², or < 25.0 kg/m²), systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C,

LDL-C, Family history of diabetes (yes/no). smoking (yes/no), alcohol consumption (yes/no), physical activity(yes/no), education (no attending school or primary school, middle school or high school, college degree or higher), income level ($<¥600$, $¥600-1000$, or $\geq ¥1000$), use of antihypertensive (yes/no for each) and lipid-lowering medications (yes/no for each)

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Table 4 Adjusted hazard ratio and 95% confidence interval for incidence of T2DM in the total population: Sensitivity analysis

	Non exposed	Famine exposure	
		Fetal	Early childhood
	1 October 1961 to 30 September 1964 (n=8912, Ref.)	1 October 1959 to 30 September 1961(n=3919)	1 October 1956 to 30 September 1959(n=9971)
Total&Sensitivity analysis(N=22802)			
# of case / participants	1605/8912	818/3919	2098/9971
Incidence (/1000 person years)	18.2	21.4	21.7
Model 1	1	1.172(1.077,1.275)	1.189(1.114,1.269)
Model 2	1	1.209(1.111,1.317)	1.153(1.079,1.231)
Model 3	1	1.195(1.097,1.302)	1.133(1.060,1.211)

Model 1: unadjusted.

Model 2: multivariate adjustment was made for sex, body mass index (≥ 30.0 kg/m², 25.0-29.9 kg/m², or <25.0 kg/m²), systolic blood pressure, diastolic blood pressure, triglycerides, HDL-C, LDL-C, family history of diabetes (yes/no).

Model 3: on the basis of model 2, smoking (yes/no), alcohol consumption (yes/no), physical activity(yes/no), education (no attending school or

primary school, middle school or high school, college degree or higher), income level ($<¥600$, $¥600-1000$, or $\geq ¥1000$), use of antihypertensive (yes/no for each) and lipid-lowering medications (yes/no for each) were further adjusted in the whole population.

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Figure 1 Trends in blood glucose levels in three groups

Trends in blood glucose levels in three groups

333x202mm (118 x 118 DPI)

Figure 2 Cumulative incidence curve of DM in three group
(log-rank $P < 0.004$)

Cumulative incidence curve of DM in three group
(log-rank $P < 0.004$)

306x276mm (118 x 118 DPI)