Association between Birthweight and Diabetes: the Role of Body Mass Index and Lifestyle in Later Life

Running Title: Association between Birthweight and Diabetes

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Abstract

Background: We aim to investigate the association between birthweight and diabetes in a Chinese population and whether body mass index (BMI) and lifestyle factors in later life affect this association.

Methods: We used data of 49118 participants aged ⩾40 years with recalled birthweight from the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, a nationwide population-based cohort. The diagnosis of diabetes was based on oral glucose tolerance test and HbA1c measurement. Logistic regression models were used to evaluate the association of birthweight and risk of diabetes in later life.

Results: Increased risk of diabetes was associated with lower or higher birthweight. The odds ratios (OR) and 95% confidence intervals (CI) of diabetes were 1.28

(1.11-1.47), 1.11 (1.04-1.19) and 1.20 (1.07-1.34), respectively, for individuals with birthweight of <2500g, 3500 to 3999g, ≥4000g, compared to those with birthweight of 2500-3499g. The significant associations were prominent in participants with current BMI ≥ 24 kg/m^2, but not detected in those with normal BMI (OR, 95%CI: 1.20, 0.96-1.49; 1.11, 0.98-1.25; and 1.10, 0.89-1.37, respectively). Moreover, individuals with low birthweight but with healthy dietary habits (OR, 95% CI: 0.94, 0.68-1.29) or ideal physical activity (OR, 95% CI: 1.41, 0.97-2.04) did not experience an elevated risk of diabetes.

Conclusions: An U-shaped association was observed between birthweight and the risk of diabetes. Healthy lifestyles (healthy dietary habits or ideal physical activity) may eliminate the negative effect of low birthweight in the development of diabetes, but not the effect of high birthweight.

Keywords: birthweight, body mass index, diabetes, lifestyle

Highlights:

Previous studies, but not all, revealed that low birthweight was significantly associated with diabetes. The association between birthweight and diabetes is controversial and the role of body mass index (BMI) and lifestyle in later life in the association remains unclear. Current study added new evidence for an U-shaped association between birthweight and the risk of diabetes. Normal BMI or healthy lifestyle may mitigate the negative effect of low birthweight in the development of diabetes.

Introduction

Diabetes mellitus (DM) has become a worldwide epidemic and the prevalence of diabetes among Chinese adults has reached to 11.6%.[1] As we known, the development of diabetes was effected by both genetic and environmental risk factors. Early life status has also been associated with the risk of diabetes in adulthood.[2] Birthweight, an indicator for early life development, has been proved to be associated with impaired glucose tolerance, insulin resistance, as well as coronary heart disease.[2]

The association between birthweight and risk of diabetes has subsequently been examined in a large number of previous investigations and remained the subject of debate. Some studies found that low birthweight increased the risk of type 2 diabetes mellitus (T2DM), and some found that individuals with high birthweight are more likely to develop diabetes in later life.[3, 4] Harder, et al [5] and Wei JN, et al [6] suggested a U-shaped and linear inverse relationship between birthweight and the risk of T2DM. In addition, it was found that the risk of diabetes was highest in people with a small birth size but with obesity in adults.[7] It is of great importance to evaluate lifestyle factors accompanied with birthweight and the risk for T2DM in different populations.

As suggested, the risk and progression of T2DM could be modified by the adoption of a healthier lifestyle.[8] Previous studies have shown that the association between low birthweight and risk of diabetes was stronger among people with unhealthy lifestyle.[9] Another study found subjects predisposed to T2DM due to a small birth size were

strongly protected from glucose intolerance by regular exercise.[10] Unhealthy lifestyles might be a strong modifier for the association between birthweight and diabetes, especially among the Chinese population who are going through a transition from traditional lifestyles to western patterns.[11] To our knowledge, there are few studies assessed the relationship of birthweight and diabetes and whether body mass index (BMI) and lifestyle in later life influence this association, in a representative nationwide cohort study in China.

In the current study, we assessed the relationship of self-reported birthweight with the risk of T2DM and the role of BMI and lifestyle in later life in the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, a representative nationwide cohort in China.

Methods

Study population

The REACTION Study is an ongoing multicenter prospective study. Details of this study have been described previously.[12-16] In brief, 259,657 participants aged 40 years or older were recruited from 25 communities in different geographic regions with different degrees of economic development across mainland China. There was no limitation on gender or ethnicity.

Among this nationwide study population, 52,369 individuals recalled their

birthweights. Individuals were eligible for inclusion in the current study if they were 40 to 80 years old and their reported birthweight ranged from 500 g to 8000 g. Also, those with no information on BMI, blood pressure, fasting blood glucose (FBG) and postprandial blood glucose (PBG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were excluded. Finally, 49118 individuals were included in the analysis (Figure 1). The REACTION study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine. Written informed consent was obtained from each individual.

Data collection

The information of sociodemographic characteristics, medical history, lifestyle factors (e.g., cigarette smoking, alcohol drinking, physical activity and dietary habits), as well as birthweight were obtained using a standard questionnaire. Body weight, height and waist circumference (WC) were measured during recruitment. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Physical activity was estimated using the Global Physical Activity Questionnaire. Dietary intake habits were assessed by a dietary score based on the recommendation of the American Heart Association, [17] according to the frequency and quantity of typical food items in the past 12 months. The dietary score included the following 4 components: fruits and vegetables $\geq$ 4.5 cups/d, fish $\geq$ two 3.5-oz servings/week, sweets/sugar-sweetened beverages $\leq$ 450 kcal/week, and soy protein $\geq$ 25 g/d. Systolic blood pressure (SBP)

and diastolic blood pressure (DBP) were measured using an automated electronic device (OMRON Model HEM-725 FUZZY, Omron Company, Dalian, China) three times at 1-min intervals after a ≥ 5-min rest, and the mean value of the three measurements was used in analysis.

Fasting blood sample was collected and all participants underwent a 75-g oral glucose tolerance test (OGTT). Glucose oxidase or hexokinase method was used to evaluate the glucose concentrations within 2 h after blood sample collection at local hospital. Sera were aliquoted and shipped in dry ice at −80 °C to the central laboratory at Shanghai Institute of Endocrine and Metabolic Diseases. This clinical laboratory is certificated by the U.S. National Glycohemoglobin Standardization Program and passed the College of American Pathologists (CAP)'s Laboratory Accreditation Program. Hemoglobin A1c was determined using high-performance liquid chromatography (VARIANT II System, Bio-Rad Laboratories, CA, USA). Triglycerides (TG), TC, HDL-C and low-density lipoprotein cholesterol (LDL-C) were measured by an autoanalyzer (ARCHITECT c16000 System, Abbott Laboratories, IL, USA).

Definitions

In this study, ever smokers included both former smokers (quit smoking for ≥ 6 months) and current smokers. Ever alcohol drinkers included both former drinkers (quit for drinking ≥ 6 months) and current drinkers. According to the criteria set for the Chinese

population,[18] overweight was defined as a BMI of 24.0–27.9 kg/m^2 and obesity was defined as a BMI ≥ 28.0 kg/m^2. Diabetes was diagnosed as FPG ≥ 126 mg/dL (7.0 mmol/L), or 2 hour glucose after 75-g OGTT ≥ 200 mg/dL (11.1 mmol/L), or HbA1c ≥ 6.5% (48 mmol/mol), or previous diagnosis of diabetes by physicians and using insulin or taking antidiabetic medications.[19] Dyslipidemia was defined as TC ≥ 6.22 mmol/L (240 mg/dL), TG ≥ 2.26 mmol/L (200 mg/dL), LDL-C ≥ 4.14 mmol/L (160 mg/dL), and HDL-C < 1.04 mmol/L (40 mg/dL).[20] Ideal physical activity was defined as moderate intensity ≥ 150 min/week or vigorous intensity ≥ 75 min/week or moderate and vigorous physical activity ≥ 150 min/week according to "2008 Physical Activity Guidelines for Americans".[21] Healthy dietary habits was defined as dietary score = 4.

Statistical analysis

Considering the distribution of birthweight in the current study and the classifications reported in previous studies,[6,22] participants were categorized into four groups according to birthweight of <2500 g, 2500–3499 g, 3500–3999 g and ⩾ 4000 g. Baseline characteristics were described according to the birthweight group. All continuous variables are presented as the mean ± Standard Deviation (SD); all categorical variables are presented as number (percentage). P-values were calculated using $\chi 2$ tests for categorical variables and linear regression analyses for continuous variables.

Logistic regression analysis was used to determine the relationships of birthweight

and diabetes using the second category of birthweight (2500-3499 g) as the reference group, i.e. considering this range as the normal birthweight. The risk estimates are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The multivariable models included age, sex, education, smoker, drinker, ideal physical activity (yes/no), healthy dietary habits (yes/no), SBP, dyslipidemia and current BMI (continuous). To demonstrate possible interactions of adulthood BMI and healthy lifestyles with birthweight in the development of diabetes, we categorized individuals into groups in logistic regression, e.g., individuals with normal birthweight and normal BMI (<24 kg/m^2), those with low birthweight and normal BMI, those with normal birthweight and obesity ($\geqslant$28 kg/m^2), and those with low birthweight and obesity. We also generated interaction terms using the cross-products of birthweight with BMI or birthweight with healthy lifestyle and assessed the interaction using the likelihood ratio test by comparing the full model including the interaction term with the reduced model excluding the interaction term. Both the full model and the reduced model contained the birthweight and the BMI/lifestyle variable, as well as the other factors described previously. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). Statistical significance was set at a two tailed $P<0.05$.

Results

The study population comprised 49,118 study participants, including 13,725 men (27.94%) and 35,393 women (72.06%). The mean age was 55.83±8.82 years. Mean

self-reported birthweight was 3073.81±451.24 g. The prevalence of low birthweight (<2500 g) was 2.27%, (1.55 % in men and 2.55 % in women). Generally, 24.43% (12,001) had diabetes, 17.86% (8774) were with general obesity, and 65.79% (32,252) were with abdominal obesity. There is significant difference in the characteristics of the included 49,118 participants versus the excluded 210,539 participants (Supplemental Table 1). The selected participants are younger, having more women and more individuals with diabetes or better dietary habits.

Baseline characteristics of the included participants by birthweight categories are shown in Table 1. With increasing birthweight, the prevalence of general obesity and central obesity increased. FBG, PBG, HbA1c, TC, HDL-C and LDL-C were highest in those with low birthweight (< 2500 g). The prevalence of diabetes was the highest in the low birthweight group (28.1%) but lowest in the normal birthweight group (24.0%).

Table 2 showed the associations of birthweight and diabetes. Compared with the normal birthweight group, individuals with lower or higher birthweight both had an increased risk of diabetes. The multivariate-adjusted OR (95% CI) of diabetes was 1.23 (1.07-1.42), 1.13 (1.06-1.21), and 1.23 (1.10-1.38), respectively, for birthweight group <2500 g, 3500-3999 g and ≥4000 g. Further adjustment for current BMI did not attenuate these associations, the adjusted OR (95% CI) was 1.28 (1.11-1.47), 1.11 (1.04-1.19), and 1.20 (1.07-1.34), accordingly. After excluding these participants with

missing data on lifestyle, the result was not changed almost (Supplemental Table 2).

Next, we assessed the combined effect of birthweight and adulthood BMI on the risk of diabetes. The prevalence of diabetes according to birthweight categories and BMI were displayed in Figure 2. The prevalence of diabetes was higher among overweight or obese individuals regardless their birthweight. As the degree of obesity increased, prevalence of diabetes increased in the same birthweight categories. Multivariate-adjusted logistic regression analysis revealed that after adjusting possible confounding factors, those with obesity or overweight had significantly increased risk for diabetes, compared with the reference group (birthweight of 2500-3499 g) with normal BMI (< 24 kg/m^2). In the overweight group, adjusted OR (95% CI) ranged from 1.47 (1.39-1.56) to 2.19 (1.76-2.72). In the obesity group, adjusted OR (95% CI) ranged from 2.08 (1.95-2.22) to 2.54 (2.02-3.19) (Table 3). Interaction existed in terms of birthweight and BMI categories (*P* for interaction <0.0001).

The association of birthweight and diabetes were also investigated in the subgroups of sex, age, healthy dietary habits (yes/no) and ideal physical activity (yes/no) (Table 4). In participants with healthy dietary habits or ideal physical activity, the increased diabetes risk of lower birthweight can be eliminated. Adjusted ORs (95%CI) of diabetes were 0.94 (0.68-1.29) and 1.41 (0.97-2.04), respectively. Compared with individuals in the reference group, only those with the birthweight of ≥ 4000 g had a significant association with diabetes. On the contrary, participants with an unhealthy

dietary habits or poor physical activity had increased risk of diabetes, regardless of the birthweight levels. When combined different condition of BMI and lifestyle, we found low birthweight was associated with a risk of diabetes only in those with abnormal BMI and unhealthy lifestyle (1.54, 1.24-1.92), compared with individuals with birthweight of 2500-3499g in the same condition of BMI and lifestyle (Supplemental Table 3). In addition, compared with participants with normal birthweight, only birthweight < 2500 g conferred a higher OR for diabetes after multivariate-adjustment among men (OR, 1.40, 95% CI, 1.04-1.89), while each birthweight categories had higher OR among women (OR, 95%CI: 1.24, 1.06-1.46 for birthweight < 2500 g, 1.14, 1.04-1.25 for birthweight 3500-3999 g, 1.29, 1.11-1.48 for birthweight ≥ 4000 g, respectively). Interaction existed in terms of birthweight and healthy dietary habits (*P* for interaction=0.024).No interaction was observed for birthweight with ideal physical activity (*P* for interaction=0.88).

Discussion

In this large cohort study, we found an U-shape association between birthweight and the risk of diabetes after adjustment for covariates, including age, sex, education, smoking status, drinking status, ideal physical activity (yes/no), healthy dietary habits (yes/no), systolic blood pressure, dyslipidemia and even current BMI. Both low birthweight and high birthweight were associated with higher risk of diabetes, despite the fact that the prevalence of obesity in later life increased with increasing levels of

birthweight. Analyzing the combined effect of birthweight and current BMI on the risk of diabetes, we observed a statistically significant association in those with obesity or overweight, but not those with normal current BMI. There is heterogeneity between sexes for the association of birthweight and diabetes. Both low birthweight and high birthweight were associated with the risk of diabetes in women, while only birthweight < 2500 g conferred a higher risk of diabetes in men. Lifestyles affect the association between birthweight and diabetes. Stratified analyses revealed a healthier lifestyle, including healthy dietary habits and ideal physical activity might eliminate the risk of developing diabetes due to low birthweight.

The association of birthweight and diabetes in current analysis was consistent with findings of some previous studies. A meta-analysis of 14 studies reported a U-shaped relation of birthweight with risk of diabetes, demonstrating that both low birthweight and high birthweight were associated with higher risk of T2DM compared to those with normal birthweight. Pooled estimates OR (95% CI) was 1.47 (1.26-1.72) for low birthweight and 1.36 (1.07-1.73) for high birthweight.[5] Another research in schoolchildren aged 6–18 years in Taiwan confirmed a U-shaped relationship between birthweight and risk of T2DM, with an adjusted-OR (95% CI) of 2.91 (1.25-6.76) for low birthweight and 1.78 (1.04-3.06) for high birthweight.[6] Studies in Pima Indians also revealed a U-shaped relationship between birthweight and risk of T2DM.[23] We confirmed this relationship in the middle-aged and elderly population of China.

However, some studies found that low birthweight but not high birthweight was a risk factor for diabetes. Forsen et al found the odds ratio for T2DM was 1.38 (95% CI, 1.15-1.66) for each 1-kg decrease in birthweight, in 3639 men and 3447 women.[24] The Black Women's Health Study found that women with very low birthweight had a 40% higher risk of diabetes and those with low birthweight had a 13% higher risk than women with normal birthweight.[25] On the contrary, a case-control study supposed that there was a significant association between high birthweight (>4000 grams) and diabetes for Saskatchewan Registered Indian (OR 1.63, 95% CI 1.20-2.24) but not low birthweight (<2500 grams).[4] Another case-control study confirmed it that the risk for T2DM increased in those with birthweight >4.2kg (OR 4.8, 95% CI 1.3-17.6 per 1 kg), but decreased with increasing birthweight until 4.2 kg (OR 0.49, 95% CI 0.37-0.66 per 1 kg).[3] The reasons for the inconsistency are not entirely clear. The difference of ethnicity and natural distributions of birth weight might play an important role. Besides，unhealthy lifestyles in later life may influence the association of birthweight and diabetes, as observed in the current analysis and also indicated by previous studys.[9] Furthermore, Gestational diabetes and healthy status during pregnancy might have a significant influence on the aboved association.[26]

In our study, we confirmed previous associations between low birthweight and diabetes. Low birthweight was a result of fetal undernutrition. Results from the Chinese famine study indicated that fetal exposure to famine increased the risk of

diabetes in adult.[27] There are some hypotheses to explain the observed association between low birthweight and diabetes, of which 'the thrifty phenotype', or 'fetal programming hypothesis' was an important one.[28, 29] The 'thrifty phenotype hypothesis' considered that as a consequence of fetal undernutrition, the infant have to be nutritionally thrifty. According to this, the thrifty phenotype would confer a survival advantage under conditions of nutritional deprivation, but a sudden move to good or over-nutrition exposes the reduced state of Beta-cell function and more prone to developing diabetes.[29] Another hypothesis that needs to be emphasized is the 'fetal insulin hypothesis',[30] which proposed that genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus as well as insulin resistance in adult life. Some studies provided evidence to the 'fetal insulin hypothesis'. Previous study found three genetic loci associated with T2DM (ADCY5, CDKAL1, and HHEX-IDE) were also associated with low birthweight.[31] This hypothesis indicated that insulin deficiency and beta cell dysfunction may already be present in fetal life. In addition, Horikoshi et al demonstrated that associations between early growth phenotypes and adult cardiometabolic disease.[32]

Besides, our study suggested that high birthweight were also associated with an increased risk for diabetes. Maternal diabetes in pregnancy which was adopted to be an important risk factor for diabetes is associated with an increased risk of macrosomia or high birthweight as well.[33] Therefore, we must to examine whether the relation of high

birthweight and diabetes was a result of maternal diabetes in pregnancy to some extent. Dyck et al [4] proposed the "hefty fetal phenotype" (or "hefty fetal type") hypothesis, which supposed that excess fetal nutrition has become the overriding intrauterine factor in the pathogenesis of T2DM and plays a pivotal role in the early stages, similar to the "thrifty genotype" hypothesis. Adair et al found a higher birthweight was associated with overweight in adult (OR, 1.28, 95% CI 1.21-1.35),[34] which was a strong risk factor of DM.

Moreover, the role of current BMI in the association of birthweight and DM remains unclear. A study from the Japanese Nurses' Health Study cohort, including 26,949 women, found that the risk of DM is high regardless of birthweight in overweight adults (BMI ≥25.0 kg/m^2), while women with normal BMI tended to have a high risk of DM when they were born with a low birthweight.[35] They pointed out that the risk of DM increased in those with low birthweight even when their adult BMI was normal. However, in the present study, we observed a significant association in those with obesity or overweight no matter what birthweight they have, but not those with normal current BMI. Also, the adjustment for adult BMI strengthened the association between low birthweight and diabetes but weakened the association for high birthweight. We found a significant interaction between birthweight and BMI category on risk of diabetes. Our findings suggested that the relation between birthweight and DM may be modified by the BMI in later life. Meanwhile，according to the "thrifty phenotype

hypothesis"[28], the thrifty phenotype is more prone to developing diabetes, when a sudden move to over-nutrition exposes the reduced state of Beta-cell function.[29] Based on the result in present study and the thrifty phenotype hypothesis, we think that it is important to avoid over-nutrition exposure for those with low birthweight. Good body size management may eliminate the increased risk of diabetes due to low birthweight. Avoidance of weight gain during adult benefit persons born with abnormal weight and may be worthwhile.

Results from subgroup analysis emphasized the importance of adult lifestyle, which was consisted with a recent study. The study including 149,794 participants from three large prospective cohorts found that fetal growth restriction and unhealthy lifestyle would increase the risk of diabetes in adult.[9] Eriksson et al found that subjects predisposed to T2DM due to low birthweight are strongly protected from glucose intolerance by regular exercise.[10] In our study, those with low birthweight but healthy dietary habits or ideal exercise did not conducted a significant increased risk of diabetes. We supposed that the risk of diabetes associated with low birthweight could be counterbalanced in those with healthy lifestyle (e.g. healthy dietary habits and ideal physical activity). People exposed to famine in utero and with a low birthweight should have an appropriate diet and avoid obesity by exercise.[36]

Strengths of this study include the large sample size and representativeness of the population aged 40 years and older across China. Still, several limitations should be

addressed. First of all, the birthweight in this study were self-reported, which may results in inevitable recall bias. Secondly, the information of overall metabolic and health status of both parents, especially during pregnancy, which might affect both birthweight and adult diabetes, were missing. Moreover, population in this study were all older than 40 years, which further limits the generalizability of the findings. Furthermore, since only 20.2% (52396/259657) of the original cohort self-reported their birthweight, subjects included in the present study may not be representative of the cohort as a whole. Comparisons between those included and excluded showed that differences in birthweight, though statistically significant, were small. In addition, the Information on lifestyle and diabetes diagnosis were collected at the same time. Overweight/obesity and unhealthy lifestyle may increase the risk of incident of T2DM. We regretted that the bias cannot be avoided due to cross-sectional nature. Also the difference between the time onset of diabetes with the birth weight cannot be analyzed. Prospective design of the study using diabetes diagnoses during follow-up is needed. Last, the diagnosis of diabetes was not based on a random plasma glucose≥200 mg/dL accompanied with the presence of classic symptoms of hyperglycemia. Nevertheless, diagnosis of diabetes based on plasma FBG and PBG is the commonest method in epidemiological studies.

In conclusion, we found that both low birthweight and high birthweight were associated with higher risk of diabetes compared to birthweight between 2500 to 3499

grams. Participants with the low birthweight and overweight in later life had the highest risk of developing diabetes. The adoption of a healthier lifestyle (e.g. healthy dietary habits and ideal physical activity) might change this association. Thus, great importance should be attached to both abnormal birthweight and healthy lifestyle to maintain non-obesity in later life in prevention of developing diabetes.

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Figure legends

Figure 1 Study selection flowchart.
BMI, body mass index; FBG, fasting blood glucose; PBG, postprandial blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

Figure 2 Prevalence of diabetes according to birthweight and current body mass index (BMI).

Table 1 Characteristics of participants according to birthweight categories

	Birthweight (grams)			
	<2500	2500-3499	3500-3999	≥4000
No. of participants (n, %)	1116 (2.3)	40875 (83.2)	5424 (11.0)	1703 (3.5)
Male (n, %)	213 (19.09)	10786 (26.39)	2155 (39.73)	571 (33.53)
Age (years)	56.46±8.95	55.80±8.80	55.94±8.96	55.57±8.71
Education>9 years (n, %)	453 (40.6)	13566 (33.2)	1881 (34.7)	854 (50.2)
Smoker (n, %)	124 (11.11)	6487 (15.87)	1282 (23.64)	338 (19.85)
Drinker (n, %)	90 (8.1)	4223 (10.3)	891 (16.4)	232 (13.6)
Ideal physical activity (n, %)	155 (13.89)	5160 (12.62)	849 (15.65)	294 (17.26)
Healthy dietary habits (n, %)	273 (24.46)	7658 (18.74)	1079 (19.89)	377 (22.14)
BMI (kg/m^2)	24.53±4.29	24.94±3.66	25.21±3.65	25.30±3.65
BMI categories (%)				
Normal weight	556 (49.82)	17066 (41.75)	2134 (39.34)	636 (37.35)
Overweight	396 (35.48)	16640 (40.71)	2198 (40.52)	718 (42.16)
Obese	164 (14.70)	7169 (17.54)	1092 (20.13)	349 (20.49)
WC (cm)	84.15±10.04	85.03±10.15	85.99±10.34	86.96±10.63
SBP (mmHg)	131.73±19.63	131.92±20.28	130.85±19.32	130.67±20.51
DBP (mmHg)	77.58±10.53	78.41±10.81	78.66±10.85	78.42±11.27
FBG (mmol/L)	6.08±1.78	6.03±1.05	6.07±1.70	6.03±1.78
PBG (mmol/L)	8.77±4.12	8.42±3.91	8.46±3.98	8.52±3.96
HbA1c (%)	6.11±1.09	6.05±1.05	6.09±1.06	6.11±1.12
TC (mmol/L)	5.14±1.21	4.85±1.17	4.70±1.17	4.81±1.16
HDL-C (mmol/L)	1.33±0.36	1.28±0.34	1.23±0.33	1.25±0.35
LDL-C (mmol/L)	3.01±0.92	2.80±0.88	2.70±0.87	2.79±0.87

Diabetes (n, %)	314 (28.1)	9789 (24.0)	1433 (26.4)	465 (27.3)
Obesity (n, %)	164 (14.7)	7169 (17.5)	1092 (20.1)	349 (20.5)
Central obesity (n, %)	709 (63.7)	26759 (65.6)	3575 (66.1)	1209 (71.2)
Dyslipidemia (n, %)	507 (45.4)	17320 (42.4)	2481 (45.7)	767 (45.0)

All continuous variables are presented as the mean ± SD; all categorical variables are presented as number (percentage). P-values were calculated using χ^2 tests for categorical variables and linear regression analyses for continuous variables. Normal weight was defined as a body mass index (BMI) < 24 kg/m^2; abdominal obesity was defined as a waist circumference ≥80 cm for women and ≥85 cm in men. Healthy dietary habits was defined as dietary score=4. The assessment of dietary score included the following 4 components: fruits and vegetables ≥ 4.5 cups/d, fish ≥ two 3.5-oz servings/week, sweets/sugar-sweetened beverages ≤ 450 kcal/week, and soy protein ≥ 25 g/d. Ideal physical activity was defined as moderate intensity ≥150 min/week or vigorous intensity ≥75 min/week or moderate and vigorous physical activity ≥150 min/week. Smoker was defined as current smoking or former smoker. Drinker was defined as current drinking or used to drink. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; PBG, postprandial blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol.

Table 2 Association of birthweight and the risk of developing diabetes in later life

	Birthweight			
	<2500 g	2500-3499 g	3500-3999 g	≥4000 g
Cases/controls *n/n* (%)	314/1116 (28.14)	9789/40875 (23.95)	1433/5424 (26.42)	465/1703 (27.3)
OR (95% CI)				

Model 1	1.24 (1.09-1.42)	1.00 (ref.)	1.14 (1.07-1.22)	1.19 (1.07-1.33)
Model 2	1.23 (1.07-1.42)	1.00 (ref.)	1.13 (1.06-1.21)	1.23 (1.10-1.38)
Model 3	1.28 (1.11-1.47)	1.00 (ref.)	1.11 (1.04-1.19)	1.20 (1.07-1.34)

Model 1: Unadjusted; Model 2: Adjusted for age, sex, smoker (current or former, yes/no), drinker (current or former, yes/no), education (≥9years/< 9years), ideal physical activity (yes/no), healthy dietary habits (yes/no), systolic blood pressure and dyslipidemia (yes/no); Model 3: Further adjusted for body mass index.

Table 3 Association of birthweight and the risk of developing diabetes stratified by current BMI

	Birthweight (grams)			
	<2500	2500-3499	3500-3999	≥4000
BMI<24	1.20 (0.96-1.49)	1.00 (ref.)	1.11 (0.98-1.25)	1.10 (0.89-1.37)

24≤BMI<28	2.19 (1.76-2.72)	1.47 (1.39-1.56)	1.56 (1.40-1.74)	1.84 (1.55-2.19)
BMI≥28	2.34 (1.68-3.27)	2.08 (1.95-2.22)	2.53 (2.22-2.90)	2.54 (2.02-3.19)

BMI, body mass index. Adjusted for age, sex, smoker (current or former, yes/no), drinker (current or former, yes/no), education (≥9years/< 9years), ideal physical activity (yes/no), healthy dietary habits (yes/no), systolic blood pressure and dyslipidemia (yes/no);

Table 4 Association of birthweight and the risk of developing diabetes according to age, sex and lifestyle

	Birthweight (grams)			
	<2500	2500-3499	3500-3999	≥4000
Age				
<60years	1.38 (1.16-1.65)	1.00 (ref.)	1.08 (0.99-1.18)	1.31 (1.13-1.51)
≥60 years	1.19 (0.95-1.48)	1.00 (ref.)	1.14 (1.02-1.26)	1.05 (0.87-1.26)
Sex				
Men	1.40 (1.04-1.89)	1.00 (ref.)	1.05 (0.94-1.16)	1.05 (0.87-1.27)
Women	1.24 (1.06-1.46)	1.00 (ref.)	1.14 (1.04-1.25)	1.29 (1.11-1.48)
Healthy dietary habits				
Yes	0.94 (0.68-1.29)	1.00 (ref.)	1.04 (0.89-1.22)	1.36 (1.07-1.74)
No	1.42 (1.21-1.66)	1.00 (ref.)	1.12 (1.04-1.21)	1.15 (1.01-1.31)
Ideal physical activity				
Yes	1.41 (0.97-2.04)	1.00 (ref.)	1.12 (0.94-1.34)	1.33 (1.01-1.74)
No	1.26 (1.08-1.47)	1.00 (ref.)	1.11 (1.03-1.19)	1.17 (1.03-1.33)

Logistic regression model was adjusted for age, sex, smoker (current or former, yes/no), drinker (current or former, yes/no), education (≥9years/< 9years), ideal physical activity (yes/no), healthy dietary habits (yes/no), systolic blood pressure, dyslipidemia (yes/no) and BMI (except for the strata variables).

Figure 1

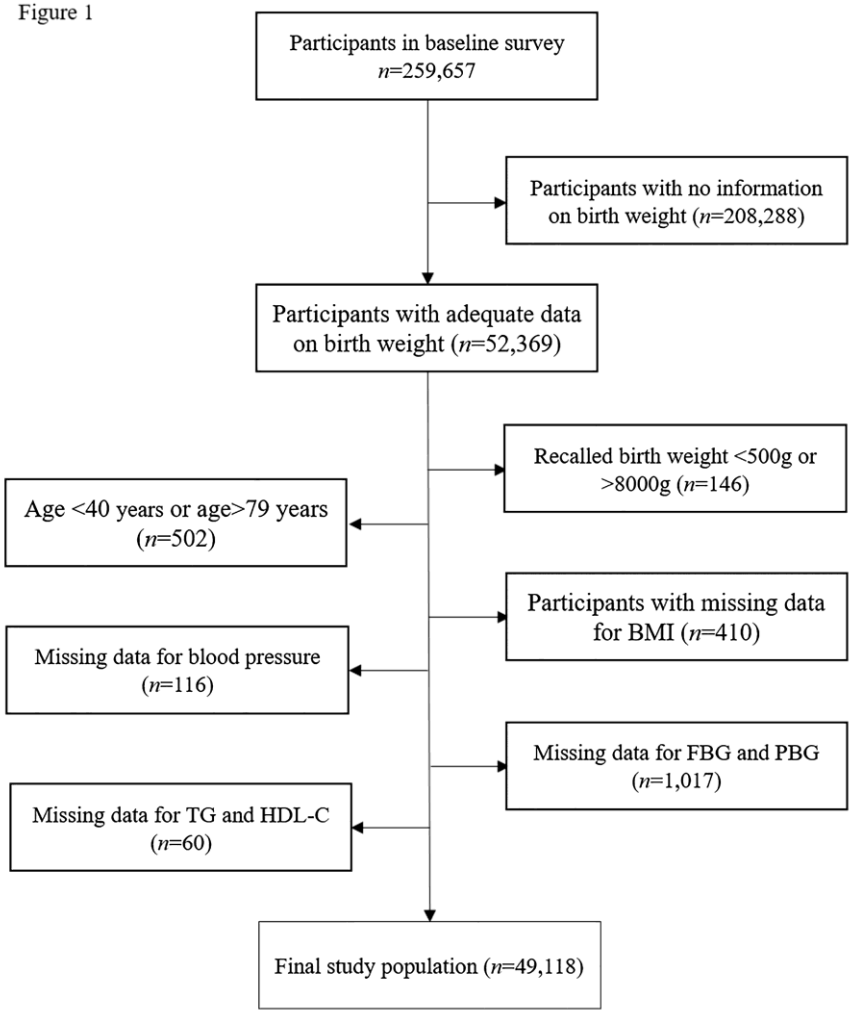

Figure 2