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Birth Measurements, Family History, and Environmental Factors Associated With Later-Life Hypertensive Status

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BACKGROUND

This birth cohort study was conducted to investigate the contribution of prenatal and antenatal environmental exposures to later-life hypertensive status.

METHODS

Two thousand five hundred and three individuals born in 1921–1954 at the Peking Union Medical College Hospital (PUMCH) were targeted; 2,081 (83.1%) participated. Clinical examinations included an interview, blood pressure (BP) measurements, and laboratory assays. Statistical analyses were performed using ordinal regression models with later-life hypertensive status as the dependent variable. Similar analyses were for subpopulations divided by family history of hypertension.

RESULTS

In the 2,081 subjects, 449 were normotensive, 531 were prehypertensive, and 1,101 had hypertension. Three hundred and forty two hypertensive patients were classified as high-risk (BP ≥180/110 mm Hg, or accompanied with diabetes or three well-established cardiovascular risk factors); the other 759 patients were at mid-to-low risks. Lower birth weight (<2,500 g: odds ratio (OR) = 1.67, $P = 0.02$; 2,500–<3,000 g: OR = 1.64, $P < 0.01$; 3,000–<3,500 g, OR = 1.40, $P = 0.01$), family history of hypertension (OR = 1.73, $P < 0.01$), poor education (OR = 1.76, $P < 0.01$), and alcoholism (OR = 3.05, $P < 0.01$) significantly predicted later-life high-risk hypertension. For participants with hypertensive family history (57.7%), the association with birth weight became nonsignificant, but poor education (OR = 2.33, $P < 0.01$) and alcoholism (OR = 3.10, $P = 0.01$) remained important. For participants without hypertensive family history (42.3%), the effects of lower birth weight (<2,500 g: OR = 2.26, $P = 0.02$; 2,500–<3,000 g: OR = 1.91, $P = 0.01$; 3,000–<3,500 g, OR = 1.78, $P = 0.01$) and alcoholism (OR = 3.23, $P < 0.01$) remained significant.

CONCLUSION

Low birth weight, low education, alcoholism, and hypertensive family history are linked to later-life hypertensive status. Low birth weight is also partly associated with one's genetic background; whereas the association with education and alcoholism are independent from hypertensive family history.

Keywords: *blood pressure; environmental exposure; family history; hypertension; hypertensive status; intrauterine development*

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The association of low birth weight with later-life hypertension has been widely reported in many geographic regions and ethnic groups.[1–4] Intrauterine under-nutrition has been hypothesized to be a risk factor for long-term metabolic, physiological, and structural modifications. It therefore programs hypertension and a range of later-life chronic disorders.[1,2,5,6] However, an alternative assumption has been suggested: that both low birth weight and later-life hypertension are phenotypes linked to the same genetic component.[7] In other words, the genetic section that codes for increased blood pressure (BP) is also responsible for intrauterine growth retardation.[8] In the present study, we examined the relationship between low birth weight and later-life hypertension, and investigated the involvement of hypertensive heredity by comparing subpopulations with and without a family history of hypertension.

In most previous studies, the clinical diagnostic criterion for hypertension (i.e., BP ≥140/90 mm Hg) was employed in data analyses. This cutoff point infers potential cardiovascular risks. Increase of BP was shown to be positively correlated with

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increased cardiovascular risk. However, BP was measured in continuous form. Those studies indicated that: higher BP generally links to greater incidence of heart attack, heart failure, stroke, and/or chronic renal dysfunction.[9] In the present study, hypertensive status was stratified for the corresponding risk of cardiovascular events based on the consensus of the seventh National Institutes of Health report on high BP[9] and the Chinese guideline for management of hypertension.[10] A variety of factors, including birth measurements, maternal records, family history of hypertension, and postnatal environmental exposures, were evaluated. The objective was to explore the associations of both prenatal and postnatal environmental exposures with later-life hypertensive status.

METHODS

Study design and target population. The target population includes individual live births at the Peking Union Medical College Hospital (PUMCH) in Beijing between 1921 and 1954, whose detailed obstetric records were available by the time of the present study.

Except for the 5-year (1942–1947) hospital closure due to World War II, a total number of 11,694 births were documented and archived in the PUMCH during the years of 1921–1941 and 1948–1954. Based on actuarial population projections, ~6,570 people were estimated to be alive when the study was scheduled. From 2003 to 2005, 2,503 individuals were actually traced through community households registries and media publicities.[11]

Of the 2,503 individuals, 175 (7.0%) had died, 78 (3.1%) refused to be surveyed, and 165 (6.6%) were living outside Beijing, resulting in 2,085 (83.3%) eligible participants.

Ethics. The study protocol was approved by the ethics committee of the PUMCH. All subjects provided written informed consent before study participation. Hypertensive patients who were identified during the study were referred to their primary healthcare provider.

Clinical examinations. Data collection was performed in the outpatient clinic of PUMCH. During the clinic visit, a team of trained and authorized research staff administered a series of standard questionnaires to the subjects. Information about demographics and lifestyle (e.g., smoking habit, alcohol use, and physical exercise) was collected. The questionnaire also addressed one's medical history, with respects to coronary heart disease, cerebral vascular disease, diabetes, dyslipidemia, renal disorders, and the related medical managements. In addition, the subjects received physical examinations, including measurements of height, weight, and BP. BP was measured after the subject was sitting for at least 5 min. The participants were instructed to avoid alcohol, cigarette smoking, caffeine-containing products, and excessive exercise for 30 min prior to the BP measurement. Based on the recommendation of the American Heart Association,[12] two BP measurements were obtained for each participant using the same standard mercury sphygmomanometer on the same arm. When the difference of the measured systolic BP or diastolic BP was larger than 5 mm Hg, a third measurement was taken[13] and the two closer measurements were averaged as the BP of record.

Terminology

Hypertension: Hypertension was diagnosed if the average systolic BP was ≥140 mm Hg and/or the average diastolic BP was no <90 mm Hg, and/or the research participant had a definite history of hypertension with or without concurrent antihypertensive treatment.[14,15]

Hypertensive status was a separate variable classified as: (i) high-risk hypertensive status; the subgroup of hypertension with high cardiovascular risks included subjects with a mean systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg, or subjects with a mean BP ≥140/90 mm Hg and concomitant diabetes or three clinically important cardiovascular risk factors (i.e., dyslipidemia, smoking, and obesity (body mass index ≥28 kg/m^2)),[16] or subjects with an average BP ≥140/90 mm Hg and presence of cardiovascular disorders (coronary heart disease, renal impairment, or cerebral vascular disease); (ii) the subgroup of hypertension with moderate to low cardiovascular risks[10] consisted of subjects who met the diagnosis for hypertension but were not assigned to subgroup 1); (iii) the subgroup of prehypertensive status was assigned to subjects who had an average BP ≤140/90 mm Hg and ≥120/80 mm Hg and was free from antihypertensive treatment, and (iv) the subgroup of normotensive status referred to subjects with optimal average BP (<120/80 mm Hg).[9] Diagnosis of diabetes was made when subject's fasting plasma glucose was ≥126 mg/dl, or the 2-hour postmeal glucose was ≥200 mg/dl, or the subject had a definite history of diabetes with or without medicine.[17] Dyslipidemia was defined as the presence of at least one of the following abnormalities: triglyceride ≥150 mg/dl, or total cholesterol ≥220 mg/dl, or low-density lipoprotein ≥100 mg/dl, or high-density lipoprotein ≤40 mg/dl. Family history of hypertension referred to subjects whose parent(s) or direct sibling(s) were known to be hypertensive. Major loss was defined as being bereft of one's spouse or child(ren).

Statistical analyses. Data management was performed with the software program EpiData (version 3.0, www.epidata.dk). The SPSS software (version 12.0; SPSS, Chicago, IL) was used for statistical analyses.

Continuous variables were treated with one-way analysis of variance with polynomial contrast, while categorical variables were compared using the χ^2-tests.

A multilevel ordinal regression model was estimated for all subjects with valid data excluding the cases with missing data of the study variables (model I) to evaluate the contribution of each factor to the later-life hypertensive status and calculate the corresponding odds ratios (OR). The four-level measure of hypertensive status was the dependent variable and the stratum of high-risk hypertension was the reference category. The independent variables consisted of birth weight (<2,500 g, 2,500–3,000 g, 3,000–3,500 g, or ≥3,500 g), ratio of biparietal diameter to birth length (≥0.2, 0.18–0.20, or <0.18), placental

weight (<450 g, 450–525 g, 525–600 g, 600–675 g, or ≥675 g), gestational weeks (<37 weeks, 37–42 weeks, or >42 weeks), gestational age (≥35 years or <35 years), parity (≥5 times, 2–4 times, or once), family history of hypertension (yes or no), years of education (≤9 years, 9–12 years, or >12 years), occupation (officer, physician, sales, labor, or others), paternal occupation (officer, physician, sales, or labor),history of alcoholism (daily alcohol consumption >150 g, or less), history of sufficient physical exercise (>5 years' daily exercise, or less), and history of major loss (yes or no). The variables birth year (1921–1936, 1937–1941, or 1948–1954) and gender (male or female) were included in model 1.

Two additional multilevel ordinal regression models were estimated for subjects with (model 2) or without (model 3) a family history of hypertension. The statistical approach was the same as the abovementioned, except that the previous independent variable "family history of hypertension" was no longer entered into the regression models.

RESULTS

Study population

Hypertensive status was obtained for 2,081 subjects: 1,021 men (49.1%) and 1,060 women (50.9%). The average age of the sample was (59.6 ± 8.2) years old. The majority of subjects (n = 1,744, 85.8%) had 9 or more years of education. Other characteristics of the participants are listed in Table 2 by hypertensive status.

Based on the obstetric records of the study participants, we compared the deceased and the survivors who did not participate in the study to the study participants. The deceased had statistically significantly smaller birth weights than participants (2,945.5 g vs. 3,108.8 g and 3,141.8 g, for the participants and nonrespondents, respectively, F = 11.03, P < 0.01), body length (48.9 cm vs. 49.4 cm and 49.6 cm, for the participants and nonrespondents, respectively, F = 3.72, P = 0.03) and head circumference (31.0 cm vs. 31.6 cm and 31.6 cm, for the participants and nonrespondents, respectively, F = 11.12, P < 0.01). However, the differences between the participants and the

Table 1 | Demographic data and parameters of interest in the four subgroups of the hypertensive status

	Total	Normotensive	Prehypertensive	Mid-low risk HTN	High-risk HTN	P value
	N = 2,081	N = 449	N = 531	N = 759	N = 342	
	Mean	Mean	Mean	Mean	Mean	
	(Min–Max)	(Min–Max)	(Min–Max)	(Min–Max)	(Min–Max)	
Birth weight (g)	3,109	3,155	3,133	3,093	3,049	0.005
	(1,270–5,330)	(1,350–5,330)	(1,700–4,410)	(1,410–4,370)	(1,270–4,835)	
Head circumference (cm)	31.6	31.8	31.6	31.5	31.6	0.053
	(20.0–44.0)	(27.7–37.0)	(23.2–40.0)	(20.0–38.0)	(26.0–44.0)	
Birth length (cm)	49.4	49.6	49.4	49.4	49.2	0.123
	(34.0–63.0)	(34.0–61.5)	(39.0–60.5)	(35.5–63.0)	(35.5–58.0)	
Placenta weight (g)	547	541	540	542	542	0.833
	(250–1,360)	(315–1,180)	(250–1,360)	(250–1,180)	(310–1,180)	
Biparietal diameter/birth length	0.19	0.19	0.19	0.19	0.19	0.427
	(0.13–0.31)	(0.15–0.29)	(0.14–0.31)	(0.13–0.24)	(0.14–0.25)	
Gestational weeks	39	39	39	39	39	0.079
	(29–53)	(31–46)	(32–53)	(29–53)	(30–48)	
Gestational age (years)	28	28	27	27	28	0.355
	(18–44)	(14–45)	(16–48)	(16–44)	(14–48)	
Parity (times)	3	2	3	2	3	0.075
	(2–13)	(2–11)	(2–13)	(2–10)	(2–9)	
Age (years)	60	57	59	61	62	<0.001
	(50–85)	(50–82)	(50–85)	(50–81)	(50–81)	
Gender (male%)	49.1	41.0	45.8	50.7	61.1	<0.001
Education (high%[a])	83.8	88.2	84.1	82.6	80.1	0.025
Occupation (labor%)	14.5	12.3	14.0	14.7	17.9	0.043
HTN family history (%)	57.2	49.8	51.6	63.9	60.9	<0.001
Alcoholism[b] (%)	3.4	2.7	1.9	3.6	6.1	0.006
Substantial exercise[c] (%)	19.8	18.6	19.8	21.3	17.9	0.522
History major loss (%)	57.8	55.4	55.4	59.8	60.2	0.219

HTN, hypertension.
[a]High education: education >9 years. [b]Alcoholism: daily alcohol consumption >150 g. [c]Substantial exercise: used to take physical exercise nearly every day for >5 years.

nonparticipating survivors were not statistically significant. Differences among the three groups with regards to gestational weeks ($F = 2.58$, $P = 0.08$), placenta weight ($F = 2.14$, $P = 0.12$), or the ratio of biparietal diameter to birth length ($F = 2.11$, $P = 0.12$) were not statistically significant.

Hypertensive status

Among the 2,081 subjects, 425 (20.4%) subjects were classified as high-risk hypertension, 676 (32.5%) had hypertension with moderate-to-low risk, 531 (25.5%) were classified as prehypertensive, and 449 (17.9%) were normotensive. Table 1 presents the demographic data and the variables of interest for the total group and the subgroups. The subgroups with higher cardiovascular risks were significantly older ($P < 0.01$) and the proportion of men was larger ($P < 0.01$). An inverse relationship between birth weight and hypertensive status was observed ($P < 0.01$): the higher cardiovascular risk the hypertensive status infers the lower the mean birth weight is. A family history of hypertension was more prevalent among those with mid-to-low or high-risk hypertension ($P < 0.01$).

Association with hypertensive status

Model 1 is based on data from 1,575 subjects (75.7%). As shown in Table 2, birth weight, family history, history of alcoholism, and educational background were statistically significant predictors of later-life high-risk hypertension: lower birth weight (<2,500 g, OR = 1.67 (1.08, 2.58), $P = 0.02$; 2,500–<3,000 g, 1.64 (1.21, 2.21), $P < 0.01$; and 3,000–<3,500 g, 1.40 (1.08, 1.82),

Table 2 | The multiordinal regression model of all subjects ($N = 1,575$) (dependent variable: hypertensive status)

					95%CI		
		s.e.	Wald	OR	Lower	Upper	*P*
Birth year (vs. 1948–1954)	1921–1936	0.136	71.698	3.16	2.42	4.12	0.000
	1937–1941	0.128	28.387	1.99	1.54	2.55	0.000
Gender (vs. male)	Female	0.096	21.454	0.64	0.53	0.77	0.000
Birth weight (vs. ≥3,500) (g)	<2,500	0.222	5.303	1.67	1.08	2.58	0.021
	2,500–3,000	0.153	10.310	1.64	1.21	2.21	0.001
	3,000–3,500	0.134	6.249	1.40	1.08	1.82	0.012
Biparietal Diameter/birth length (vs. <0.18)	≥0.2	0.167	3.712	0.72	0.52	1.01	0.054
	0.18–0.20	0.110	1.047	0.89	0.72	1.12	0.306
Placenta weight (vs. ≥675) (g)	<450	0.189	0.263	1.10	0.76	1.60	0.608
	450–525	0.171	0.849	0.85	0.61	1.19	0.357
	525–600	0.173	1.125	0.83	0.59	1.17	0.289
	600–675	0.188	0.002	0.99	0.69	1.43	0.964
Gestational weeks (vs. <37)	>42	0.293	0.216	0.87	0.49	1.55	0.642
	37–42	0.190	2.160	0.76	0.52	1.10	0.142
Gestational age (vs. ≤35) (years)	>35	0.174	0.191	1.08	0.77	1.52	0.662
Parity (vs. 1) (times)	2–4	0.157	0.213	1.08	0.79	1.46	0.644
	≥5	0.104	0.596	1.08	0.88	1.33	0.440
Heredity (vs. no)	Yes	0.094	34.175	1.73	1.44	2.09	0.000
Alcoholism (vs. no) &	Yes	0.298	14.008	3.05	1.70	5.46	0.000
Exercise (vs. yes)+	No	0.118	0.005	0.99	0.79	1.25	0.942
Education (vs. >12) (years)	≤9	0.176	10.290	1.76	1.25	2.49	0.001
	9–12	0.139	2.581	1.25	0.95	1.64	0.108
Parental job (vs. labor)	Officer	0.190	2.626	0.74	0.51	1.07	0.105
	Physician	0.183	0.979	0.83	0.58	1.19	0.322
	Sales	0.195	1.292	0.80	0.55	1.17	0.256
Job (vs. labor)	Officer	0.188	0.003	1.01	0.70	1.46	0.954
	Doctor	0.194	0.142	1.08	0.73	1.57	0.706
	Sales	0.225	0.087	1.07	0.69	1.66	0.767
	Other	0.384	1.073	0.67	0.32	1.42	0.300
Major loss (vs. no)	Yes	0.157	2.587	1.29	0.95	1.75	0.108

Link function: Logit. Model fitting information: $P < 0.001$; goodness-of-fit: Pearson $P = 0.676$, deviance $P = 1.000$.
Test of parallel lines: $P = 0.590$. Items in the brackets are the reference condition of the corresponding variable used in the regression.
CI, confidence interval; OR, odds ratio.

Table 3 | The multiordinal regression model of subjects with family history of hypertension (*N* = 908, 57.7%) (dependent variable: hypertensive status)

					95%CI		
		s.e.	Wald	OR	Lower	Upper	*P*
Birth year (vs. 1948–1954)	1921–1936	0.183	43.257	3.34	2.33	4.78	<0.001
	1937–1941	0.170	15.411	1.95	1.40	2.72	<0.001
Gender (vs. male)	Female	0.127	17.714	0.59	0.46	0.75	<0.001
Birth weight (vs. >3,500) (g)	<2,500	0.300	0.794	1.31	0.73	2.35	0.373
	2,500–3,000	0.206	3.208	1.45	0.97	2.16	0.073
	3,000–3,500	0.180	0.966	1.19	0.84	1.70	0.326
Biparietal Diameter/birth length (<vs. 0.18)	≥0.2	0.223	1.562	0.76	0.49	1.17	0.211
	0.18–0.20	0.146	0.249	0.93	0.70	1.24	0.618
Placenta weight (vs. ≥675) (g)	<450	0.251	0.055	1.06	0.65	1.73	0.815
	450–525	0.230	1.273	0.77	0.49	1.21	0.259
	525–600	0.236	0.756	0.81	0.51	1.29	0.385
	600–675	0.254	0.115	0.92	0.56	1.51	0.734
Gestational weeks (vs. <37)	>42	0.390	0.026	0.94	0.44	2.02	0.873
	37–42	0.257	2.032	0.70	0.42	1.15	0.154
Gestational age (vs. ≤35) (years)	>35	0.241	0.319	1.15	0.71	1.84	0.572
Parity (vs. 1) (times)	2–4	0.217	0.058	1.05	0.69	1.61	0.810
	≥5	0.138	1.083	1.15	0.88	1.51	0.298
Alcohol (vs. no)	Yes	0.458	6.080	3.10	1.26	7.61	0.014
Exercise (vs. yes)	No	0.157	0.209	1.07	0.79	1.46	0.647
Education (vs. >12) (years)	≤9	0.239	12.528	2.33	1.46	3.72	0.000
	9–12	0.186	2.038	1.30	0.91	1.88	0.153
Parental job (vs. labor)	Officer	0.261	0.449	0.84	0.50	1.40	0.503
	Doctor	0.251	0.197	0.89	0.55	1.46	0.657
	Sales	0.266	0.166	0.90	0.53	1.51	0.684
Job (vs. labor)	Officer	0.251	0.023	1.04	0.64	1.70	0.879
	Doctor	0.257	0.465	1.19	0.72	1.98	0.495
	Sales	0.303	0.603	0.79	0.44	1.43	0.437
	Other	0.469	2.095	0.51	0.20	1.27	0.148
Major loss (vs. no)	Yes	0.213	0.628	1.18	0.78	1.80	0.428

Link function: Logit. Model fitting information: $P < 0.001$; goodness-of-fit: Pearson $P = 0.616$, deviance $P = 1.000$.
Test of parallel lines: $P = 0.689$. Items in the brackets are the reference condition of the corresponding variable used in the regression.
CI, confidence interval; OR, odds ratio.

$P < 0.01$), family history of hypertension (OR = 1.73 (1.44, 2.09), $P < 0.01$), poor education (i.e., ≤9 school years; OR = 1.76 (1.25, 2.49), $P < 0.01$), and alcoholism (i.e., daily consumption ≥150 g, OR = 3.05 (1.70, 5.46), $P < 0.01$).

Model 2 (Table 3) provides results for the subpopulations with a family history of hypertension. The association between birth weight and later-life high-risk hypertension was not significant; whereas shorter educational years (OR = 2.33 (1.46, 3.72), $P < 0.01$) and history of alcoholism (OR = 3.10 (1.26, 7.61), $P = 0.014$) remained negatively related to later-life high-risk hypertension.

In contrast, for those without a family history of hypertension (model 3) (Table 4), the associations with lower birth weight (<2,500 g, OR = 2.26 (1.17, 4.38), $P = 0.02$; 2,500–<3,000 g, OR = 1.91 (1.20, 3.02), $P = 0.01$; 3,000–<3,500 g, OR = 1.78 (1.19, 2.68), $P = 0.01$) and alcoholism (OR = 3.23 (1.47, 7.07), $P < 0.01$) remained statistically significant. The association with low education, however, was not statistically significant.

The characteristics of the valid cases included in model 1 were compared to those of the cases with missing data. Later-life hypertensive status between the two datasets was compared. The percentage composition of hypertensive status (normotensive%, prehypertensive%, low-to-middle risk hypertension%, high-risk hypertension%) did not differ significantly between the cases with missing data (23.1%, 23.1%, 36.2%, 17.6%) and those included in

Table 4 | The multiordinal regression model of subjects without family history of hypertension (*N* = 667, 42.3%) (dependent variable: hypertensive status)

					95%CI		
		s.e.	Wald	OR	Lower	Upper	*P*
Birth year (vs. 1948–1954)	1921–1936	0.208	29.160	3.07	2.04	4.61	<0.001
	1937–1941	0.201	12.508	2.04	1.37	3.02	<0.001
Gender (vs. male)	Female	0.151	4.932	0.72	0.53	0.96	0.026
Birth weight (vs. >3,500) (g)	<2,500	0.337	5.854	2.26	1.17	4.38	0.016
	2,500–3,000	0.235	7.541	1.91	1.20	3.02	0.006
	3,000–3,500	0.207	7.782	1.78	1.19	2.68	0.005
Biparietal Diameter/birth length (vs. <0.18)	≥0.2	0.259	1.943	0.70	0.42	1.16	0.163
	0.18–0.20	0.171	0.850	0.85	0.61	1.19	0.357
Placenta weight (vs. ≥675) (g)	<450	0.296	0.146	1.12	0.63	2.00	0.703
	450–525	0.259	0.026	0.96	0.58	1.59	0.872
	525–600	0.260	0.579	0.82	0.49	1.37	0.447
	600–675	0.288	0.076	1.08	0.62	1.90	0.783
Gestational weeks (vs. <37)	>42	0.459	0.451	0.73	0.30	1.81	0.502
	37–42	0.290	0.502	0.81	0.46	1.44	0.478
Parity (vs. 1) (times)	2–4	0.259	0.213	0.89	0.53	1.48	0.645
	≥5	0.234	0.129	1.09	0.69	1.72	0.720
Gestational age (vs. ≤35) (years)	>35	0.161	0.007	0.99	0.72	1.35	0.932
Alcoholism (vs. no)	Yes	0.400	8.584	3.23	1.47	7.07	0.003
Exercise (vs. yes)	No	0.184	0.336	0.90	0.63	1.29	0.562
Education (vs. >12) (years)	≤9	0.267	0.828	1.28	0.76	2.15	0.363
	9–12	0.213	0.441	1.15	0.76	1.75	0.506
Parental job (vs. labor)	Officer	0.282	2.092	0.66	0.38	1.16	0.148
	Doctor	0.273	0.487	0.83	0.48	1.41	0.485
	Sales	0.294	0.945	0.75	0.42	1.34	0.331
Job (vs. labor)	Officer	0.292	0.022	0.96	0.54	1.70	0.883
	Doctor	0.304	0.086	0.91	0.50	1.66	0.769
	Sales	0.341	1.483	1.51	0.78	2.95	0.223
	Other	0.698	0.286	1.45	0.37	5.70	0.593
Major loss (vs. no)	Yes	0.239	2.109	1.41	0.89	2.26	0.146

Link function: Logit. Model fitting information: $P < 0.001$; goodness-of-fit: Pearson $P = 0.428$, deviance $P = 1.000$.
Test of parallel lines: $P = 0.477$. Items in the brackets are the reference condition of the corresponding variable used in the regression
CI, confidence interval; OR, odds ratio

model 1 (21.1%, 26.3%, 36.6%, 16.1%) ($P = 0.96$). As for the birth measures of the two datasets, no statistically significant difference were detected in their birth records (mean of model 1 dataset vs. mean of non-model 1 dataset, *P* value) (birth weight: 3,117.0 g vs. 3,082.7 g, $P = 0.15$; birth length: 49.5 cm vs. 49.2 cm, $P = 0.05$; head circumference: 31.6 cm vs. 31.6 cm, $P = 0.46$; placenta weight: 541.8 g vs. 543.9 g, $P = 0.77$; gestational weeks: 39.2 vs. 39.1, $P = 0.49$; ration of biparietal diameter to birth length: 0.187 vs. 0.186, $P = 0.29$). Thus, we expect that excluding the cases with missing data would not cause any substantive biases.

DISCUSSION

To our knowledge, this is the first study that investigates the association of birth measurements with later-life hypertensive status. The definition of different hypertensive statuses are based on their related cardiovascular risks. In comparison with values of BP or a simple classification of hypertension by single-visit BP measurement and/or self-report medical history, such a multilevel-dependent variable of hypertensive status better reflects the continuous relationship between BP and cardiovascular risk and is, therefore, employed by Chinese guideline for hypertension and the present study.

Four factors are demonstrated significantly related to later-life hypertensive status: (i) low birth weight is associated with hypertensive status in individuals without hypertensive family and has a smaller effect size in the total population; (ii) family history of hypertension is an independent risk factor for later-life high-risk hypertension; (iii) history of alcoholism raises the probability of high-risk later-life hypertension in the total population, regardless of the existence of hypertensive family history;

(iv) high levels of education act as be a protective factor in the total population, as well as in the subpopulation with hypertensive family history. Despite the lack of genetic measures, these findings are thought to imply the contribution of heredity to later-life hypertension. Moreover, the results provide information on the roles of prenatal and adulthood exposure. The inverse relationship between birth weight and later-life hypertensive status is consistent with the observations in populations of diverse ages and regions.[18,19] The association between low birth weight and later-life hypertension is neutralized in the subpopulation with hypertensive family history. Since family history of hypertension was taken as a surrogate indicator for hypertensive heredity in the study, involvement of genetic background seems to be an explanation. However, the lack of genetic measures makes the findings less conclusive.

Similar findings have been reported in some twin studies. Ljzerman *et al.* observed an inverse relationship between intrapair birth weight difference and intrapair difference in BP in dizygotic, but not monozygotic, twins. Since monozygotic twins share almost identical genes, the genetic difference with dizygotic twins was thought to explain the above distinction regarding birth weight–BP relationships.[8] The same researchers reported that an increase in sympathetic activity was an intermediary factor bridging low birth weight and hypertension. The association pattern was similar to that observed in the previous study.[8] Thus low birth weight, increased sympathetic activity, and increased BP were thought to be three different phenotypes that are derived from certain identical genetic factors.[20] Besides, Jaquet *et al.* found that small for gestational age experienced by both mother and father would significantly raise the risk of their offspring being small for gestational age and father's birth outcomes are as important as maternal birth outcomes for their infant's fetal growth. These findings suggest the impact of genetic factors on low birth weight.[21] Nevertheless, our findings also support the famous "fetal origin" theory.[1] In the subgroup without a family history of hypertension, low birth weight appeared to "program" later-life hypertension. The poor intrauterine environment during the "critical" period of visceral growth is likely to be the underlying reason.[22]

There is a negative relationship between education and later-life hypertensive status. Because higher education is typically linked to better socioeconomic conditions and more awareness of cardiovascular risks, well-educated individuals were expected to be at lower risk of cardiovascular events. We also found the association with education to be larger in the subpopulation with a family history of hypertension. One explanation for this pattern is that a family history of hypertension increases disease awareness among well-educated individuals. For the total sample, a history of alcoholism significantly increases hypertensive risk. The ORs for variable "alcoholism" are of similar size in the two subgroups based on family history of hypertension. Thus the association between alcoholism and later-life hypertension is not influenced by one's family history of hypertension.

The target population of this study was sampled from individuals born in PUMCH during 1921–1954. All participants were investigated during their mid- to late-life. The strength of it is the acquisition of relatively complete life profiles from subjects. However, the inevitable limitation is the high proportion of unreachable potential participants due to death or major migration.[11] As one of the oldest western hospitals in China, PUMCH has gained a good reputation for medical service in China since the early 20th century. The hospital served a wide socioeconomic spectrum but higher on average than the general Chinese population.[11] As a result, >80% of the study participants are well-educated, which is much higher than the average educational attainment of the Chinese elderly but is close to that of US elderly[23] and modern Chinese urban population. In this respect, the results of the present study might predict the effects of hereditary and environmental factors on the future later-life hypertension of today's young population.

The birth measures of the missed individuals were comparable to those of the study participants, but the birth size of deceased individuals is significantly smaller than the participants, implying a positive relationship between birth size and life expectancy. Moreover, in our study, the proportion of patients with hypertension is very similar to the prevalence of hypertension in the general Chinese population aged between 55 and 74 years.[24] These facts warrant the sample selection of the present study.

We also evaluated the effect of missing data for the statistical models estimated. In case individuals with both normal birth weight and high-risk hypertension, or individuals with both low birth weight and normotensive status were supposed disproportionately missing from the three models, hence the results reported here would be selection-biased. On the contrary, included cases and excluded cases did not significantly differ, however, in either later-life hypertensive status or birth weight.

In conclusion, birth weight, education, and alcoholism, as well as family history of hypertension, are linked to later-life hypertensive status. In addition to intrauterine under-nutrition, the association between low birth weight and later-life hypertensive status is partly mediated by one's genetic background. On the other hand, two adulthood environmental/behavioral exposures, education and alcoholism, are found to affect later-life hypertensive status independent of the hypertensive heredity.

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