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# Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study

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## ABSTRACT

### OBJECTIVES

To prospectively assess the joint association of birth weight and established lifestyle risk factors in adulthood with incident type 2 diabetes and to quantitatively decompose the attributing effects to birth weight only, to adulthood lifestyle only, and to their interaction.

### DESIGN

Prospective cohort study.

### SETTING

Health Professionals Follow-up Study (1986-2010), Nurses' Health Study (1980-2010), and Nurses' Health Study II (1991-2011).

### PARTICIPANTS

149 794 men and women without diabetes, cardiovascular disease, or cancer at baseline.

### MAIN OUTCOME MEASURE

Incident cases of type 2 diabetes, identified through self report and validated by a supplementary questionnaire. Unhealthy lifestyle was defined on the basis of body mass index, smoking, physical activity, alcohol consumption, and the alternate healthy eating index.

### RESULTS

During 20-30 years of follow-up, 11709 new cases of type 2 diabetes were documented. The multivariate adjusted relative risk of type 2 diabetes was 1.45 (95% confidence interval 1.32 to 1.59) per kg lower birth weight and 2.10 (1.71 to 2.58) per unhealthy lifestyle factor. The relative risk of type 2 diabetes associated with a combination of per kg lower birth weight and per unhealthy lifestyle factor was 2.86 (2.26 to 3.63), which was more than the addition of the risk associated with each individual factor, indicating a significant interaction on an additive scale (P for

interaction<0.001). The attributable proportions of joint effect were 22% (95% confidence interval 18.3% to 26.4%) to lower birth weight alone, 59% (57.1% to 61.5%) to unhealthy lifestyle alone, and 18% (13.9% to 21.3%) to their interaction.

### CONCLUSION

Most cases of type 2 diabetes could be prevented by the adoption of a healthier lifestyle, but simultaneous improvement of both prenatal and postnatal factors could further prevent additional cases.

## Introduction

Diabetes has become a worldwide epidemic, with an estimated 387 million people living with diabetes and 4.9 million attributable deaths in 2014.<sup>1</sup> Type 2 diabetes represents about 85-95% of all cases of diabetes.<sup>1</sup> Unhealthy lifestyles, in concert with genetic susceptibility, have been implicated in the rapid rise of type 2 diabetes.<sup>2,3</sup> Early life development has also been associated with risk of type 2 diabetes in adulthood.<sup>4,5</sup> Previous evidence has shown that exposure to severe starvation or stress in utero is associated with an elevated risk of hyperglycemia or type 2 diabetes later in life.<sup>6,7</sup> Low birth weight, a widely used indicator for growth retardation, has been associated with glucose intolerance, a lesser insulin secretory capacity, and increased risk of type 2 diabetes.<sup>8-10</sup>

In addition, the relation between early life exposures and later life risk of metabolic disorders such as type 2 diabetes may be modified by lifestyle in adulthood.<sup>6,7,11-13</sup> Previous studies have shown that the association between low birth weight and risk of type 2 diabetes was stronger among people who were overweight as adults,<sup>11,12</sup> and the association between prenatal exposure to famine and risk of type 2 diabetes was stronger among people following the Western dietary pattern.<sup>7</sup> Participants with a small birth size experienced more protection from glucose intolerance through exercising regularly.<sup>13</sup> However, these studies examined only dietary factors or exercise,<sup>7,13</sup> and very few of them analyzed potential interactions between prenatal and postnatal factors. Therefore, we prospectively assessed the joint association of birth weight and established lifestyle risk factors in adulthood with incident type 2 diabetes,<sup>2</sup> applying both multiplicative interaction and additive interaction analyses that are more relevant to public health measures. Our analyses were based on the detailed data from three large ongoing prospective cohorts, the Health Professionals Follow-up Study (HPFS),<sup>14</sup> the Nurses' Health Study (NHS),<sup>12</sup> and the NHS II.<sup>15</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Both unhealthy lifestyles and early life development have been implicated in the rapid rise of type 2 diabetes

Previous studies suggest that the relation between early life exposures and later life risk of metabolic disorders such as type 2 diabetes may be modified by lifestyle in adulthood

However, very few studies have comprehensively explored the joint effect of prenatal and postnatal factors on risk of diabetes

## WHAT THIS STUDY ADDS

The data provide consistent evidence for synergistic effects of birth weight, a widely used indicator for growth retardation, and adulthood lifestyle factors on risk of type 2 diabetes

## Methods

### Study population

The HPFS,<sup>14</sup> NHS,<sup>12</sup> and NHS II<sup>15</sup> were established in 1986, 1976, and 1989, respectively. Detailed information on lifestyle habits and medical history is updated biennially. Participants in HPFS, NHS, and NHS II completed an initial food frequency questionnaire in 1986, 1980, and 1991, respectively, which serves as the baseline for this analysis. Food frequency questionnaires were updated approximately every four years thereafter.

The analysis reported here included 149 794 participants who were free of cardiovascular disease, cancer, and diabetes at baseline; provided birth weight data; and had no missing data on diet, physical activity, smoking, alcohol consumption, or body weight at baseline.

### Ascertainment of type 2 diabetes

Cases of type 2 diabetes were identified by self reported diabetes and confirmed by a validated supplementary questionnaire.<sup>2 16</sup> For cases before 1998, we applied the National Diabetes Data Group criteria to confirm type 2 diabetes.<sup>17</sup> We used the American Diabetes Association diagnostic criteria for confirmation from 1998 onward.<sup>18</sup>

The validity of self reported type 2 diabetes diagnosis in our cohorts has been previously documented in detail and in both women and men.<sup>16 19</sup> In a random sample of 62 cases in NHS that were confirmed by the supplementary questionnaire, 61 (98%) cases were reconfirmed after their medical records were reviewed by an endocrinologist blinded to the supplementary questionnaire.<sup>19</sup> In HPFS, of 59 cases who reported newly diagnosed diabetes between 1996 and 1998, 57 (97%) were reconfirmed by medical records.<sup>16</sup> Moreover, we did another sub-study to assess the specificity of self reported diabetes status. In a random sample of participants (n=200) who reported no diabetes, only one (0.5%) participant had an elevated fasting plasma glucose or plasma fructosamine concentration in the diabetic range, and her concentrations were barely above the diagnostic cut-offs.<sup>20</sup>

### Ascertainment of birth weight

Participants in the HPFS, NHS, and NHS II cohorts were asked to provide their birth weight on the 1994, 1992, and 1991 questionnaires, respectively, within categories (in lb) of under 5.0, 5.0 to 5.5, 5.6 to 7.0, 7.1 to 8.5, 8.6 to 10.0, over 10.0, and unknown in NHS and under 5.5, 5.5 to 6.9, 7.0 to 8.4, 8.5 to 9.9, 10.0 or over, and unknown in NHS II/HPFS.<sup>12 14 15</sup> We excluded the participants without birth weight information. Thus, the categories of birth weight in this analysis were (in kg): under 2.5, 2.5-3.15, 3.16-3.82, 3.83-4.5, and over 4.5.

Validation studies have been reported previously.<sup>14</sup> In brief, birth weight was collected from both the man and his mother for 3803 participants from HPFS. The mean birth weight reported by the HPFS participants was 7.65 (SD 1.25) lb; that reported by their mothers was 7.63 (1.17) lb. The Spearman correlation coefficient for the participants' self reported birth weight and birth

weight reported by the mother was 0.71 (P<0.001). The frequency of the mother and participant reporting exactly the same birth weight category was 68.6%. In 97.9% of the participants, the birth weight categories as self reported or reported by the mothers were within one category of each other.<sup>14</sup>

In another validation study in NHS II,<sup>21</sup> the birth weight of 220 randomly chosen women was obtained from state birth certificates and was classified according to the five categories of birth weight that were reported on the 1991 NHS II questionnaire. Seventy per cent of participants reported the same birth weight category as that listed on their birth certificate. The Spearman correlation coefficient between categories of self reported and certificate derived birth weight was 0.74.<sup>21</sup> Women in NHS and NHS II were also asked to report whether they were born two or more weeks premature (before due date—that is gestational period  $\leq 37$  weeks).

### Definition of unhealthy and healthy lifestyle

We included five lifestyle factors in our unhealthy lifestyle score—diet, smoking, physical activity, alcohol consumption, and body mass index—on the basis of the strength of evidence in relation to risk of type 2 diabetes.<sup>2</sup> For each unhealthy lifestyle factor, the participant received a score of 0 if he or she met the criterion for low risk and 1 otherwise. This unhealthy lifestyle score was significantly associated with risk of type 2 diabetes in our previous study.<sup>2</sup> As we focused on the effect of adulthood modifiable lifestyle habits on type 2 diabetes, we did not include clinical risk factors such as blood pressure and cholesterol.

We created a summary dietary score based on the alternate healthy eating index 2010, which is based on a high consumption of vegetables, fruit, nuts and legumes, whole grains, long chain fats, and poly-unsaturated fatty acids and a low consumption of sugar sweetened drinks and fruit juice, red/processed meat, trans fat, and sodium.<sup>22</sup> We defined a healthy diet as a diet score in the top 40% of each cohort distribution. For smoking, we defined low risk as currently not smoking. We included former smokers in the healthy category because our focus was on modifiable risk factors. For physical activity, we classified low risk as at least 30 minutes a day of moderate or vigorous activity. We defined moderate alcohol consumption as 5-15 g/day for women and 5-30 g/day for men, consistent with guidelines for moderate alcohol intake in the United States. We defined low risk body mass index below 25.

### Statistical analysis

Participants contributed person time from the return of the baseline questionnaire (HPFS, 1986; NHS, 1980; NHS II, 1991) until the date of diagnosis of type 2 diabetes, death, loss to follow-up, or the end of the follow-up period (30 January 2010 for HPFS; 30 June 2010 for NHS, and 30 June 2011 for NHS II), whichever came first. We used multivariable time dependent Cox proportional hazards models to estimate relative risk and 95% confidence interval. The time scale for the left truncated

survival model was age (months), which was additionally stratified by calendar time in two year groups.

For the association between birth weight and risk of type 2 diabetes, we selected participants in the middle category of birth weight (3.16-3.82 kg) as the reference group. We quantified a linear trend across birthweight categories with a Wald test for linear trend by assigning the median value to each category and modeling this variable as a continuous variable. We assessed a potential non-linear relation of birth weight with risk of type 2 diabetes by using restricted cubic spline transformations without prior specification of the risk function.<sup>23</sup> We did tests for non-linearity by using the likelihood ratio test and compared the model with the linear term only with the model with both the linear and cubic spline terms. We adjusted the multivariable models for suspected confounding factors including ethnicity, family history of diabetes, living alone or with others, marital status, menopausal status and postmenopausal hormone therapy use for women, smoking status, alcohol consumption, physical activity and alternate healthy eating index. In a secondary analysis, we also further adjusted for adulthood body mass index. As we did not collect data on full term or preterm birth in men, in our main analysis we included all participants on the basis of their birthweight category regardless of whether they were preterm or full term birth. In the sensitivity analyses based on women only (NHS and NHS II), we classified the participants into seven categories of birth weight (preterm and birth weight <2.5 kg; preterm and birth weight ≥2.5 kg; full term birth weight <2.5, 2.5-3.15, 3.16-3.82, 3.83-4.5, and >4.5 kg).

We also classified participants according to the joint categories of birth weight and the number of unhealthy lifestyle factors. We used updated levels of lifestyle factors to calculate the unhealthy lifestyle score in which type 2 diabetes was predicted from the information derived from the most recent questionnaire. For example, in NHS, we examined cases of type 2 diabetes that occurred between 1980 and 1982 in relation to unhealthy lifestyle score based on risk factors reported on the 1980 questionnaire, cases occurring between 1982 and 1984 in relation to unhealthy lifestyle score based on risk factors reported on the 1982 questionnaire, and so forth (for the dietary alternate healthy eating index, it was updated every four years). We applied the same analytic strategy to HPFS and NHS II. If data were missing at a given time point, we used data from the previous cycle. We evaluated whether the associations between birth weight and type 2 diabetes differed by adulthood lifestyle by using multiplicative and additive interaction analyses.<sup>24-26</sup> We tested the multiplicative interaction by comparing the  $-2 \log$  likelihood of the multivariate adjusted models with and without the cross product interaction term.<sup>24</sup>

To access the additive interaction between birth weight and unhealthy lifestyle on risk of type 2 diabetes, we considered birth weight and count of unhealthy lifestyle factors as two continuous variables. We assessed the relative excess risk due to interaction as an index of additive interaction.<sup>26,27</sup> We further examined

the decomposition of the joint effect—that is, the proportions attributable to birth weight alone, to unhealthy lifestyle alone, and to their interaction.<sup>26,27</sup>

We also calculated the hypothetical population attributable risk, an estimation of the percentage of incident type 2 diabetes in the study population that theoretically would not have occurred if all people had been in the low risk category, combining a healthy birth weight and a healthy lifestyle, assuming a causal relation. To allow valid calculation of population attributable risk, we used pooled logistic regression models with age and time period included in the model. For these analyses, we used a single binary categorical variable and compared participants in the low risk category with the rest of the population to calculate the population attributable risk.<sup>28</sup>

We assessed the proportional hazards assumption with a likelihood ratio test comparing the model with and without an interaction term between time period and the joint category of birth weight and unhealthy lifestyle. We pooled the relative risks from the multivariate adjusted models in each cohort to obtain a summarized risk estimate with the use of an inverse variance weighted, random effect meta-analysis, and we used the Cochrane Q statistic and the  $I^2$  statistic to examine the heterogeneity of associations among the cohorts.

We used SAS version 9.3 to analyze data. Statistical significance was set at a two tailed  $P < 0.05$ .

### Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

### Results

Table 1 shows the age adjusted characteristics of the three cohorts according to five birthweight categories. Within each cohort, the prevalence of the lifestyle variables at baseline was similar across categories of birth weight. Birth weight above 4.5 kg was more common in participants with a family history of diabetes.

We documented 11 709 new cases of type 2 diabetes during 20-30 years of follow-up. We observed a consistent association between low birth weight and risk of type 2 diabetes in all the three cohorts. Compared with people in the middle category of birth weight (3.18-3.82 kg), the multivariate adjusted relative risk of type 2 diabetes among those with the lowest birth weight (<2.5 kg) was 1.49 (95% confidence interval 1.39 to 1.60). Further adjustment for current body mass index amplified the association between low birth weight and type 2 diabetes, with a pooled relative risk of 1.55 (1.46 to 1.64) (table 2).

Each unhealthy lifestyle factor was significantly associated with risk of type 2 diabetes after simultaneous adjustment in the multivariate adjusted model (supplementary table A). We further classified the participants according to the joint categories of birth weight and the number of unhealthy lifestyle factors, with the group of birth weight 3.16-3.82 kg and at least

Table 1 | Age adjusted characteristics of participants according to birthweight category

Characteristics*	Birthweight category (kg)				
	<2.5	2.5-3.15	3.16-3.82	3.83-4.5	>4.5
<b>Health Professionals Follow-up Study 1986 (n=18 305)</b>					
No (%)	885 (4.8)	4169 (22.8)	8686 (47.5)	3257 (17.8)	1308 (7.1)
Age, years	51.6	50.8	50.9	51.6	55.2
Body mass index, kg/m <sup>2</sup>	25.3	25.2	25.4	25.9	26.2
Total energy intake, kcal/d	1972	1996	2032	2057	2040
Alternate healthy eating index	46.9	46.9	46.8	46.2	47.1
Alcohol intake, g/d	10.9	11.0	11.8	11.8	11.1
Current smoking, %	8.9	8.0	8.9	9.2	10.5
Moderate to vigorous intensity exercise, h/wk	2.6	3.0	3.1	2.8	3.1
Family history of diabetes, %	23.0	21.6	20.5	23.6	24.4
<b>Nurses' Health Study 1980 (n=49 757)</b>					
No (%)	5271 (10.6)	15 416 (31.0)	22 497 (45.2)	5467 (11.0)	1106 (2.2)
Age, years	45.0	45.0	45.1	46.1	48.2
Body mass index, kg/m <sup>2</sup>	24.2	23.8	24.3	24.7	25.4
Pre-menopausal, %	60.2	60.2	61.0	59.7	57.8
Total energy intake, kcal/d	1546	1566	1576	1566	1553
Alternate healthy eating index	31.4	31.1	31.1	31.3	31.6
Alcohol intake, g/d	6.0	6.4	6.6	6.4	6.3
Current smoking, %	27.0	26.7	26.8	28.3	29.9
Moderate to vigorous intensity exercise, h/wk	4.0	4.0	4.1	4.0	3.9
Family history of diabetes, %	19.9	18.1	18.9	21.1	28.4
<b>Nurses' Health Study II 1991 (n=81 732)</b>					
No (%)	6356 (7.8)	24 807 (30.4)	39 601 (48.5)	9958 (12.2)	1010 (1.2)
Age, years	36.6	36.0	36.0	35.6	36.1
Body mass index, kg/m <sup>2</sup>	24.5	24.3	24.5	25.0	25.9
Pre-menopausal, %	95.8	96.6	96.6	96.6	97.2
Total energy intake, kcal/d	1794	1779	1799	1803	1798
Alternate healthy eating index	44.1	43.9	43.9	43.9	44.4
Alcohol intake, g/d	3.0	3.1	3.2	3.0	2.8
Current smoking, %	13.1	12.1	11.9	11.6	10.0
Moderate to vigorous intensity exercise, h/wk	2.4	2.4	2.4	2.4	2.6
Family history of diabetes, %	17.4	15.4	15.8	17.3	27.0

\*Means for continuous variables and percentage for categorical variables.

four unhealthy lifestyle factors as the reference. Compared with the reference group, participants with the birth weight of 3.83-4.5 kg and no or one unhealthy lifestyle factors had the lowest risk of developing type 2 diabetes (relative risk 0.08, 0.05 to 0.12). The graded increasing risk of type 2 diabetes with increasing number of unhealthy lifestyle factors seemed to be consistent across all the five birth weight categories (figure), which was consistently observed in all three cohorts (supplementary table B). Tests for multiplicative interactions were not significant (P for multiplicative interaction >0.9).

We found significant additive interactions between low birth weight and the number of unhealthy lifestyle factors (P for additive interaction <0.0001 for all cohorts). The multivariate adjusted relative risk of type 2 diabetes was 1.45 (1.32 to 1.59) per kg lowering of birth weight, 2.10 (1.71 to 2.58) per unhealthy lifestyle factor and 2.86 (2.26 to 3.63) for the joint effect, with a relative excess risk due to interaction of 0.31 (0.16 to 0.47). The attributable proportions of joint effect were 22% (95% confidence interval 18.3% to 26.4%) to birth weight alone, 59% (57.1% to 61.5%) to unhealthy lifestyle alone, and 18% (13.9% to 21.3%) to their interaction (table 3). The relative excess risk due to interaction was relatively

higher in NHS II (0.56, 0.32 to 0.80) than in NHS (0.30, 0.18 to 0.41) and HPFS (0.19, 0.10 to 0.29). In age stratified analysis, the relative excess risk due to interaction was 1.62 (0.47 to 2.76) among participants under 45 years old and 0.13 (0.01 to 0.24) among those aged 75 or older (supplementary figure A).

Compared with the rest of the cohorts, men and women with four healthy lifestyles including healthy dietary pattern, physically active, non-smoking, and drinking moderate alcohol combined with normal birth weight (2.5-4.5 kg) had a relative risk of diabetes of 0.42 (0.35 to 0.51). The population attributable risk for not being in this low risk group was 57%; that is, 57% of the new cases of diabetes in our cohorts could have potentially been prevented if people had healthy lifestyle factors of diet, physical activity, smoking, and drinking and with normal birth weight. When we further included keeping a healthy body mass index as a healthy lifestyle, the estimation of population attributable risk was 91%; however, only 1.91% of the study population was in this lowest risk group (table 4). The population attributable risk for not being in the lowest risk group was relatively higher in women than men (93.5% in NHS, 93.7% in NHS II, and 80.7% in HPFS).

Table 2 | Multivariate relative risks of type 2 diabetes according to birth weight

Cohorts	Birthweight category (kg)					P (non-linear)*	P (linear trend)†
	<2.5	2.5-3.15	3.16-3.82	3.83-4.50	>4.5		
<b>Health Professionals Follow-up Study (1986-2010)</b>							
Cases/person years	108/17 898	424/86 673	708/18 2310	268/67 843	95/26 629	–	–
Incidence rate (per 10 <sup>5</sup> PY)	603	489	388	395	357	–	–
Age adjusted RR (95% CI)	1.57 (1.28 to 1.92)	1.27 (1.12 to 1.43)	1.0 (ref)	1.01 (0.88 to 1.17)	0.85 (0.69 to 1.05)	0.13	<0.0001
Multivariable adjusted‡	1.47 (1.20 to 1.80)	1.25 (1.11 to 1.41)	1.0 (ref)	0.97 (0.84 to 1.11)	0.79 (0.64 to 0.99)	0.58	<0.0001
Further adjusted for BMI§	1.50 (1.22 to 1.84)	1.29 (1.14 to 1.46)	1.0 (ref)	0.87 (0.75 to 1.00)	0.69 (0.55 to 0.85)	0.88	<0.0001
<b>Nurses' Health Study (1980-2010)</b>							
Cases/person years	758/138 448	1689/414 272	2291/607 644	514/146 799	129/29 042	–	–
Incidence rate (per 10 <sup>5</sup> PY)	548	408	377	350	444	–	–
Age adjusted RR (95% CI)	1.47 (1.35 to 1.59)	1.09 (1.02 to 1.16)	1.0 (ref)	0.92 (0.84 to 1.01)	1.13 (0.94 to 1.35)	0.0002	<0.0001
Multivariable adjusted‡	1.43 (1.32 to 1.55)	1.09 (1.02 to 1.16)	1.0 (ref)	0.87 (0.79 to 0.96)	0.97 (0.81 to 1.16)	0.0258	<0.0001
Further adjusted for BMI§	1.52 (1.40 to 1.65)	1.21 (1.14 to 1.29)	1.0 (ref)	0.82 (0.75 to 0.90)	0.85 (0.71 to 1.02)	0.66	<0.0001
<b>Nurses' Health Study II (1991-2011)</b>							
Cases/person years	544/114 262	1597/454 040	2028/731 388	492/183 778	64/18 376	–	–
Incidence rate (per 10 <sup>5</sup> PY)	476	352	277	268	348	–	–
Age adjusted RR (95% CI)	1.67 (1.51 to 1.83)	1.27 (1.19 to 1.36)	1.0 (ref)	1.00 (0.90 to 1.10)	1.26 (0.98 to 1.62)	<0.0001	<0.0001
Multivariable adjusted‡	1.58 (1.44 to 1.74)	1.25 (1.17 to 1.34)	1.0 (ref)	0.95 (0.86 to 1.05)	1.06 (0.83 to 1.36)	0.009	<0.0001
Further adjusted for BMI§	1.60 (1.46 to 1.76)	1.33 (1.25 to 1.42)	1.0 (ref)	0.88 (0.79 to 0.97)	0.90 (0.70 to 1.16)	0.62	<0.0001
<b>Pooled results based on meta-analysis (random effect model)</b>							
Multivariable adjusted‡	1.49 (1.39 to 1.60)	1.19 (1.07 to 1.32)	1.0 (ref)	0.92 (0.86 to 0.98)	0.93 (0.80 to 1.09)	0.04	<0.0001
P for heterogeneity¶	–	–	–	–	–	–	0.19
Further adjusted for BMI§	1.55 (1.46 to 1.64)	1.27 (1.19 to 1.36)	1.0 (ref)	0.85 (0.80 to 0.90)	0.81 (0.69 to 0.94)	0.62	<0.0001
P for heterogeneity¶	–	–	–	–	–	–	0.46

BMI=body mass index; PY=person years; RR=relative risk.

\*Linear trend across birthweight categories was quantified with Wald test for linear trend by assigning median value to each category and modeling this variable as continuous variable.

†Potential non-linear relation of birth weight with risk of type 2 diabetes was tested using likelihood ratio method by comparing model with linear term only with model with both linear and cubic spline terms.

‡Multivariable adjusted relative risk estimated from Cox proportional hazards models; adjusted for age, ethnicity (white, yes/no), marriage status (married, divorced/separated/single, widowed); living status (alone or not), family history of diabetes (yes/no), menopausal status (premenopausal or postmenopausal (never, past, or current menopausal hormone use), women only), smoking status (never smoker, former smoker, current smoker: 1-14, 15-24, ≥25 cigarettes/d), alcohol drinking (0, 0.1-4.9, 5.0-14.9, 15.0-19.9, 20.0-29.9, ≥30 g/d), exercise (0, 0.01-1.0, 1.0-3.5, 3.5-6.0, ≥6 h/week), and alternate healthy eating index (fifth).

§Further adjusted for body mass index (<21, 21-24.9, 25-29.9, 30-31.9, ≥32).

¶Test for between study heterogeneity.

In a sensitivity analysis, we found similar associations of preterm low birth weight (relative risk 1.54, 1.41 to 1.69) and full term low birth weight (1.50, 1.39 to 1.62) with risk of type 2 diabetes. In addition, we observed a similar pattern of joint effects (supplementary figure B, top) and additive interactions with unhealthy lifestyle factors (supplementary figure B, bottom) among women with preterm low birth weight and full term low birth weight. We also observed a marginally significant association between a higher birth weight (>4.5 kg) and type 2 diabetes in women with a significant non-linear trend in age and multivariate adjusted models, which was not significant after further adjustment for body mass index (table 2). However, we found no significant additive interaction between higher birth weight and unhealthy lifestyle on risk of type 2 diabetes (supplementary figure B, bottom). The tests for the proportional hazards assumption did not indicate a violation of the assumption in either cohort.

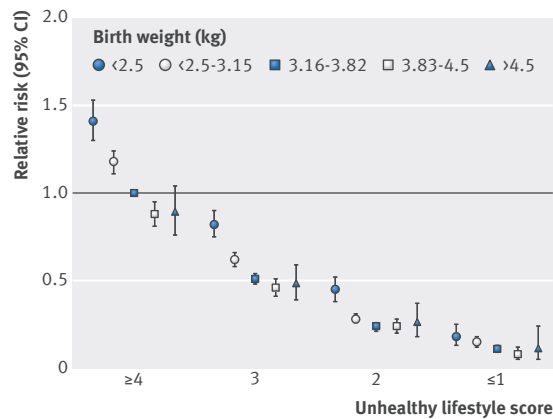
## Discussion

In three large cohorts, low birth weight and unhealthy adulthood lifestyles were jointly related to an increased risk of type 2 diabetes. The joint effect could be decomposed to 22% for a lower birth weight alone, 59% for an unhealthier lifestyle alone, and 18% for an additive

interaction between low birth weight and unhealthy lifestyle, which highlights the importance of modifiable lifestyle factors in the prevention of type 2 diabetes.

## Results in relation to other studies

Our study based on three large cohorts indicates that, theoretically, most cases of diabetes in the population would be preventable by adherence to a low risk lifestyle in adulthood combined with a healthy birth weight. The estimation of population attributable risk was relatively higher in women than men (94% of women and 81% of men). Our findings emphasize the importance of healthy lifestyle in prevention of type 2 diabetes, which is consistent with our previous finding.<sup>2</sup> The previous study indicated that a total of 91% of cases of type 2 diabetes could be attributed to the five unhealthy lifestyles in NHS.<sup>2</sup> In our new analyses, the population attributable risk was 94% in women (NHS/NHS II) and 81% in men (HPFS) for the combination of five unhealthy lifestyles and unhealthy birth weight. Differences in population attributable risk between the NHS/NHS II and HPFS cohorts warrant further research. One potential reason is the sex difference in the effect of prenatal and adulthood risk factors, which had been reported in previous studies.<sup>29-31</sup> In our analysis, both the main effect of low birth weight and unhealthy



**Multivariate relative risks of type 2 diabetes according to joint categories of birth weight and unhealthy lifestyle based on the pooled data from three cohorts (Health Professionals Follow-up Study 1986-2010, Nurses' Health Study 1980-2010, Nurses' Health Study II 1991-2011). Unhealthy lifestyles include currently smoking, exercise <30 min/d at moderate intensity, diet in bottom three fifths of alternate healthy eating index, body mass index  $\geq 25$ , and not moderate alcohol consumption (moderate: 5-15 g alcohol/d in women, 5-30 g alcohol/d in men). Cox proportional hazards models was adjusted for age, sex, ethnicity (white, yes/no), marriage status (married, divorced/separate/single, widowed), menopausal status (premenopausal or postmenopausal (never, past, or current menopausal hormone use), women only), family history of diabetes, and living status (alone or not)**

lifestyle and their additive interaction were relatively stronger among women (NHS/NHS II) than men (HPFS). The participants in the NHS II cohort were younger than those in NHS, who were younger than the men in HPFS. Our sensitivity analysis stratified by age also indicated that the relative excess risk due to interaction between lower birth weight and unhealthy lifestyle on risk of type 2 diabetes was more pronounced in younger than older participants. The fraction of disease attributable to modifiable lifestyle factors decreasing with age had been observed in a previous study, in which the relation

between lifestyle factors and hypertension was weaker in older than younger women.<sup>32</sup>

We confirmed previous associations between low birth weight (<2.5 kg) and type 2 diabetes.<sup>10</sup> Furthermore, we observed a marginally significant association between higher birth weight (>4.5 kg) and type 2 diabetes in women. Similar to a previous report,<sup>33</sup> adjustment for lifestyle factors and adult body mass index strengthened the association between low birth weight and type 2 diabetes in our study but attenuated the positive association for higher birth weight.<sup>33</sup> The pathway leading to type 2 diabetes may be different in people with low and high birth weight.<sup>34</sup> Low birth weight reflects preterm birth or intrauterine growth restriction, which may induce poor development of pancreatic  $\beta$  cell mass and function,<sup>35</sup> retarded skeletal muscle development,<sup>36</sup> and changed set point of the hypothalamic-pituitary-adrenal axis,<sup>37</sup> as well as genetic or epigenetic alterations.<sup>38,39</sup> Macrosomic infants, on the other hand, may be a reflection of excessive maternal weight gain, gestational diabetes, or prolonged gestation.<sup>40,41</sup> Recent findings indicated that high birth weight, not low birth weight, was associated with a higher adulthood body mass index,<sup>42</sup> suggesting that adulthood body mass index may be a mediator for the association between high birth weight and type 2 diabetes but not for the association between low birth weight and type 2 diabetes. In men, we observed a linear inverse association between birth weight and type 2 diabetes, which was consistent with the meta-analysis of 16 studies.<sup>10</sup>

### Potential mechanisms

Fetal growth restriction has long term physiological and structural effects that predispose people to a high disease risk in later life.<sup>4</sup> The Dutch and Chinese famine studies indicated that fetal exposure to famine was associated with early onset and increased risk of hyperglycemia or type 2 diabetes.<sup>67</sup> The fetal origins of type 2 diabetes were also indirectly supported by the consistent associations between low birth weight and a higher risk of type 2 diabetes.<sup>10</sup> However, whether the higher

**Table 3 | Attributing effects to additive interaction between birth weight and lifestyle on risks of type 2 diabetes\***

	Health Professionals Follow-up Study	Nurses' Health Study	Nurses' Health Study II	Pooled cohorts	P for heterogeneity†
<b>Main effects</b>					
Lower birth weight (per kg)	1.36 (1.09 to 1.68)	1.44 (1.26 to 1.64)	1.51 (1.28 to 1.78)	1.45 (1.32 to 1.59)	0.73
Unhealthy lifestyle‡ (per score)	1.71 (1.50 to 1.96)	2.10 (1.91 to 2.31)	2.55 (2.28 to 2.84)	2.10 (1.71 to 2.58)	<0.0001
Joint effect	2.26 (2.00 to 2.52)	2.84 (2.66 to 3.01)	3.62 (3.41 to 3.83)	2.86 (2.26 to 3.63)	<0.0001
<b>Relative excess risk due to interaction</b>					
Relative excess risk due to interaction	0.19 (0.10 to 0.29)	0.30 (0.18 to 0.41)	0.56 (0.32 to 0.80)	0.31 (0.16 to 0.47)	0.01
P value	<0.0001	<0.0001	<0.0001	0.0001	–
<b>Attributable proportion, %</b>					
Lower birth weight	28.2 (17.2 to 39.2)	23.9 (19.3 to 28.4)	19.5 (15.4 to 23.7)	22.4 (18.3 to 26.4)	0.20
Unhealthy lifestyle‡	56.5 (49.5 to 63.6)	60.0 (56.8 to 63.4)	59.1 (55.8 to 62.3)	59.3 (57.1 to 61.5)	0.66
Additive interaction	15.3 (11.0 to 19.6)	16.1 (13.7 to 18.5)	21.4 (18.1 to 24.7)	17.6 (13.9 to 21.3)	0.02

\*Multivariable adjusted relative risk estimated from Cox proportional hazards models; adjusted for age, ethnicity (white, yes/no), marriage status (married, divorced/separate/single, widowed); living status (alone or not), family history of diabetes (yes/no), menopausal status (premenopausal or postmenopausal (never, past, or current menopausal hormone use), women only).

†Test for between studies heterogeneity.

‡Unhealthy lifestyles include currently smoking, exercise <30 min/d at moderate intensity, diet in bottom three fifths of alternate healthy eating index, body mass index  $\geq 25$ , and not moderate alcohol consumption (moderate: 5-15 g alcohol/d in women, 5-30 g alcohol/d in men).

**Table 4 | Population attributable risk of type 2 diabetes associated with birth weight and adulthood lifestyles based on pooled population of three cohorts**

Low risk categories	% of population	No of cases of diabetes	Relative risk* (95% CI)	Population attributable risk†
<b>Pooled cohorts</b>				
Birth weight 2.5-4.5 kg plus:				
Three healthy lifestyles‡	10.1	518	0.55 (0.50 to 0.60)	43.0 (38.0 to 47.7)
Four healthy lifestyles§	2.75	101	0.42 (0.35 to 0.51)	57.2 (48.3 to 64.9)
Five healthy lifestyles¶	1.91	19	0.09 (0.05 to 0.14)	91.2 (86.3 to 94.4)
<b>Health Professionals Follow-up Study</b>				
Birth weight 2.5-4.5 kg plus:				
Three healthy lifestyles‡	9.02	78	0.65 (0.51 to 0.82)	35.5 (20.7 to 48.6)
Four healthy lifestyles§	4.24	26	0.44 (0.29 to 0.64)	55.6 (36.4 to 70.3)
Five healthy lifestyles¶	2.51	8	0.19 (0.10 to 0.38)	80.7 (62.8 to 90.6)
<b>Nurses' Health Study</b>				
Birth weight 2.5-4.5 kg plus:				
Three healthy lifestyles‡	8.66	212	0.58 (0.50 to 0.66)	40.2 (32.0 to 47.8)
Four healthy lifestyles§	2.18	39	0.48 (0.35 to 0.66)	51.5 (34.8 to 65.0)
Five healthy lifestyles¶	1.58	5	0.06 (0.03 to 0.15)	93.5 (84.7 to 97.3)
<b>Nurses' Health Study II</b>				
Birth weight 2.5-4.5 kg plus:				
Three healthy lifestyles‡	11.7	228	0.51 (0.44 to 0.58)	45.8 (38.7 to 52.4)
Four healthy lifestyles§	2.83	36	0.38 (0.27 to 0.52)	62.0 (48.0 to 72.8)
Five healthy lifestyles¶	2.04	6	0.06 (0.03 to 0.14)	93.7 (86.2 to 97.2)

\*Relative risks compared people in low risk category with rest of population based on pooled data of three cohorts; adjusted for sex, age (in 5 year categories), time periods, presence of family history of diabetes, cohorts, and lifestyle factors not included in subgroup categories (five lifestyle factors included smoking status, exercise, alternate healthy eating index (AHEI) score, body mass index, and alcohol consumption).

†Population attributable risk is percentage of cases of type 2 diabetes in population that would theoretically not have occurred if all people had been in low risk category for these factors.

‡AHEI score in upper two fifths and moderate to vigorous exercise  $\geq 30$  min/d and non-smoking.

§AHEI score in upper two fifths and moderate to vigorous exercise  $\geq 30$  min/d and non-smoking and moderate alcohol.

¶AHEI score in upper two fifths and moderate to vigorous exercise  $\geq 30$  min/d and non-smoking and moderate alcohol and body mass index  $< 25$ .

risk of type 2 diabetes associated with low birth weight could be counterbalanced by an adulthood healthy lifestyle is not clear. Our study provides evidence that fetal growth restriction may interact with later lifestyle to increase adulthood risk of diabetes. This finding is in line with previous observations. For example, our previous famine study indicated that the association between fetal exposure to the Chinese famine and risk of hyperglycemia was exacerbated by a Western dietary pattern during adulthood.<sup>7</sup> The effect of regular exercise on glucose intolerance was found to depend on birth size, being strongest among people with a small body size at birth.<sup>13</sup> Those findings suggested that newborns with prenatal exposure to malnutrition may be more sensitive to unhealthy lifestyles in later life. Poor nutritional conditions in a pregnant woman may influence the development of the fetus to prepare for survival in an environment in which resources are scarce. When the adaptive response to starvation during the fetal period is mismatched with exposure to an affluent environment later in life, it can increase the risk of type 2 diabetes in adulthood.<sup>5</sup>

#### Public health impact

We found a significant additive interaction between birth weight and unhealthy lifestyle on risk of type 2 diabetes. Additive interaction is more relevant to public health measures than is multiplicative interaction.<sup>43</sup> Our study based on three large cohorts indicates that 18% of type 2 diabetes among a population with a lower birth weight and unhealthier lifestyle could be

attributed to additive interaction between a lower birth weight and an unhealthy lifestyle. This finding means that 18% of cases of diabetes would occur if both lower birth weight and unhealthier lifestyle were present but not if only one was present,<sup>27 44</sup> implying that a certain percentage of type 2 diabetes cases depend on both prenatal and later life factors. The significant additive interaction also indicates that the public health consequence of unhealthy lifestyle would be larger in low birthweight populations.

#### Strengths and limitations

Strengths of this study include the large number of incident cases of type 2 diabetes, long term follow-up, and consistent findings across three separate cohorts. To our knowledge, this study is the first to investigate how fetal and adulthood risk factors are jointly related to risk of type 2 diabetes. Another important strength is the high follow-up rate. In each two or four year cycle of the survey in our cohorts, follow-up rates have averaged 94%.

A limitation of the study was the lack of information on maternal factors that might influence birth weight, such as maternal gestational diabetes and weight gain during pregnancy.<sup>40</sup> Gestational diabetes was associated with both increased birth weight and increased risk of type 2 diabetes in the offspring.<sup>33 45</sup> Gestational diabetes explains most of the excess in risk of type 2 diabetes observed in macrosomia but only a small proportion of the excess risk associated with low birth weight.<sup>33 45 46</sup> Also, we could not rule out the possibility



that low birth weight is an indicator of a high genetic susceptibility to type 2 diabetes. A recent genome-wide association meta-analysis identified seven loci associated with birth weight, and two (ADCY5 and CDKAL1) of the seven loci were also associated with type 2 diabetes.<sup>38</sup> We acknowledge that low birth weight itself is not a causal risk factor in the fetal programming of adult disease but an indicator of intrauterine adversity that increases the risk of type 2 diabetes in adulthood. We did not have information on duration of gestation and thus could not determine whether the relation between low birth weight and type 2 diabetes was due to intrauterine growth retardation or premature birth with weight appropriate for gestational age. However, in our sensitivity analysis of NHS/NHS II cohorts, we found that both the main effect of birth weight and its interaction with unhealthy lifestyle on the risk of type 2 diabetes were similar in low birthweight women who were born at term and those born two weeks or more prematurely.

Our estimate of joint effect decomposition is based on the hypothesized linear associations between birth weight and type 2 diabetes as well as between unhealthy lifestyle and type 2 diabetes, which may not be generalizable in other study populations. Also, our cohorts included only health professionals, mostly white men and women,<sup>12 14 15</sup> which further limits the generalizability of the findings. However, the relative homogeneity of the study population in educational attainment and socioeconomic status enhances the internal validity. In addition, we cannot exclude the possibility of exposure misclassification of the questionnaire based assessment of lifestyle factors. However, the prospective study design indicates that such bias would likely be random with respect to outcome status, resulting in attenuation of the effect estimates and thus underestimation of the true associations. Another limitation is that our study relied on self reported birth weight. As discussed previously, missing birthweight data or misclassification of self reported birth weight was unlikely to have caused the associations we observed.<sup>7</sup>

The population attributable risk is a population specific calculation that is dependent on the prevalence of the exposure and its association with disease risk with an assumed causal effect. We acknowledge that our estimation of population attributable risk has several limitations. Firstly, as with all the observational research, although we have carefully controlled for the potential bias such as confounding, the results did not necessarily indicate causal effects. However, previous randomized clinical trials have provided support for the role of lifestyle intervention in preventing type 2 diabetes.<sup>47 48</sup> Secondly, only 1.9% of the study population fell into the healthiest lifestyle-birthweight category; however, the graded decreasing risk of type 2 diabetes with improvement of birth weight or healthy lifestyles, as shown in the figure, implies that any improvement would result in certain benefit. Thirdly, we acknowledge that the small size of the lowest risk category (19 incident events) might lead to uncertainty in our estimates. Further studies are warranted to

verify our findings. Fourthly, in our study, body mass index was the largest single contributor to the hypothetical population attributable risk, accounting for nearly 40% of the observed attributable risk. Such observations indicate that keeping a healthy body weight is the most powerful strategy for prevention of diabetes; our data also suggest that improvements in birth weight and lifestyle would add further protective effects. Fifthly, as both the prevalence of unhealthy lifestyle and the percentage of low birth weight are greater in the general US population than in our cohorts,<sup>49 50</sup> the population attributable risk in our study might underestimate the burden of prenatal and adulthood risk factors on risk of type 2 diabetes.

## Conclusion

In summary, we found that both low birth weight and unhealthy lifestyle were associated with a significantly higher risk of type 2 diabetes, and the effects of low birth weight combined with the unhealthy lifestyle score were more than the addition of the risks associated with each individual factor. The finding suggests that most cases of type 2 diabetes could be prevented by the adoption of a healthier lifestyle, but simultaneous improvement of both prenatal and postnatal factors could further prevent additional cases.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organization for the submitted work other than those detailed above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard School of Public Health. Completion of the self administered questionnaire was considered to imply informed consent.

**Transparency statement:** The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data sharing:** No additional data available.

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