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Original Article

Investigating the Relationship between Birthweight and Breast Cancer from A Non-Linear and Mediation Perspective

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Abstract

Background: Epidemiological studies have shown a positive relationship between birthweight and breast cancer; however, inconsistent, sometimes even controversial, observations emerged. We re-explored the association between them in the UK Biobank cohort.

Methods: Relying on the UK Biobank cohort data of white British volunteers recruited between 2006 and 2010 (5,760 cases and 162,778 controls), we evaluated the causal mediation between birthweight and breast cancer, with age of menarche and age at menopause as two potential mediators under the traditional mediation analysis framework. The non-linear relationship between birthweight and breast cancer was also investigated by including the square of birthweight or discretized birthweight categories (<2.5, 2.5~4.0, or >4.0). Furthermore, we performed a stratification analysis in terms of the menopause status.

Results: Birthweight can indirectly influence breast cancer risk in adulthood via the path of age of menarche or age at menopause, and found statistical evidence supporting the existence of suggestive non-linear association between birthweight and breast cancer (β=0.062 and P=0.004 for the square of birthweight) although failing to discover a linear relationship (P=0.230). We also demonstrated such non-linear association seemed more pronounced and robust for premenopausal women compared with postmenopausal ones (27.5% vs. 19.5% increase in breast cancer risk).

Conclusion: This study provided an in-depth insight into the observed relationship between birthweight and breast cancer and revealed that non-linear impact and causal mediation commonly drive the connection between the two traits.

Keywords: Breast cancer; Birthweight; UK Biobank; Non-linear association; Mediation analysis

Introduction

Over the past few decades, the relationship between breast cancer and early growth/development, perinatal intrauterine environments has been attracted much research attention, forming the well-known hypothesis that breast cancer might, to a certain extent, originate in utero (1-3). Indeed, it has been revealed that exposing to higher levels of endogenous estrogen in utero is pathophysiologically associated with increased risk of breast cancer (1, 2, 4), offering a meaningful complementary interpretation to the natural etiology of breast cancer.

As it is difficult or unrealistic to obtain pregnancy estrogen measurements retrospectively for women who have already developed breast cancer in adulthood, some indicators of high estrogen exposure are therefore employed as surrogate measures. Among those, birthweight, which is positively correlated with pregnancy estrogen concentrations, is intensively studied in the literature (If needed, please contact the author to provide). For example, a positive correlation between women's birthweight and breast cancer risk was discovered in the cohorts of two USA nurses' health studies (5); a meta-analysis of 18 epidemiological studies indicated that women born with weight >4kg had 20% (95% confidence intervals [CIs] 8-34%) higher risk of breast cancer than those born with weight <3kg (6), or 7% (95%CIs 2-12%) increased risk per 1kg, in agreement with results obtained from other meta-studies (7). Similar findings were identified in other countries and regions including a Norway study (8), Denmark studies (9-11), Britain studies (12, 13), as well as a black women's health study (14). This positive association between birthweight and breast cancer risk was further supported by the observation in the study of opposite-sexed twins (4) and the animal experiment (15).

Although the studies described above have demonstrated the existence of a relationship between high birthweight and increased risk of breast cancer, some others failed to replicate such connection or even demonstrated inconsistent correlations in effect direction, making it difficult to draw a definitive conclusion on the causal association between birthweight and breast cancer. Furthermore, previous work focused primarily on the linear relationship between birthweight and breast cancer, it is not clear whether there exists a non-linear or mediating connection between them (12, 16). For instance, individuals with birthweight <2.5kg had a 30% higher risk and individuals with birthweight >4.0kg had a 70% higher risk of breast cancer compared with those with normal birthweight (2.5-4.0kg) (3), implying that both low and high birthweight might increase the risk of this type of cancer (3, 9, 15); however, a formal analysis is relatively lacking for such relationship.

The present work attempts to assess the relationship between birthweight and breast cancer using large-scale data available from the UK Biobank cohort (17). To this aim, we first conducted a mediation analysis with age of menarche and age at menopause as two candidate mediators that stand on the path from birthweight to breast cancer. Then, we evaluated the non-linear relationship between birthweight and breast cancer to study the influence of birthweight on breast cancer. The flow diagram of data process and statistical analysis for the present study is illustrated in Fig. 1.

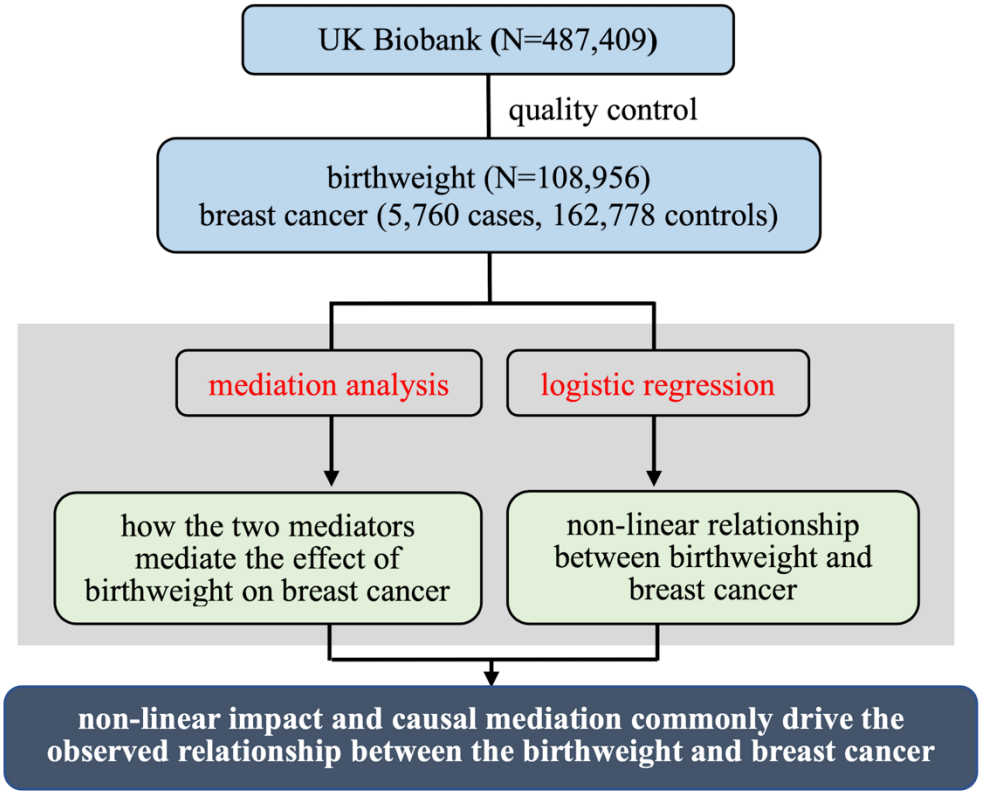

Fig. 1: Flow diagram of data process and statistical analysis for the present study. Quality control: exclude breast cancer patients whose age at menopause was earlier than age at menarche and remove patients whose age at diagnosis was prior to age at menarche or age at menopause

Methods

Individual-level UK Biobank dataset

We applied the UK Biobank data to investigate the influence of birthweight on breast cancer (17) between 2006 and 2010, with age of menarche and age at menopause as two candidate mediators. After performing the similar quality control procedure described in prior work (18), we obtained 337,198 independent individuals of white British ancestry aged 48-82 yr. We only kept female individuals with breast cancer as cases, leaving 7,350 breast cancer patients. To guarantee the temporal ordering between age of menarche, age at menopause and breast cancer, which is necessary for the causal interpretation of effects in the causal inference (19, 20), we ensured that no breast cancer patients reported their age at menopause earlier than age at menarche, and excluded 1,590 patients whose age at diagnosis was prior to age at menarche or age at menopause. Afterwards, we reserved 5,760 breast cancer patients. To maximize the sample size for boosting power, we included all female individuals without breast cancer as controls, leading to 162,778 controls. Besides birthweight, age of menarche, age at menopause and status of breast cancer, we primarily incorporated age (by the end of the last data collection), menopause or not, ever smoked or not and BMI as potential covariates (Table 1).

Table 1: Descriptive statistics of the UK Biobank data after quality control used in the mediation analysis

Variable	*N*	*Mean ± sd (yes/no)*
Birthweight (kg)	108,956	3.2 ± 0.6
Age at menarche (year)	163,763	13.0 ± 1.6
Age at menopause (year)	96,098	49.8 ± 5.0
Age (yr)	168,539	66.5 ± 7.9
Bmi (m/kg^2)	130,635	27.0 ± 5.1
Breast cancer	168,538	5,760/162,778
Menopause or not	141,969	102,889/39,080
Ever smoked or not	167,983	93,396/74,587

Note: BMI: body mass index; *N*: the sample size of diverse variables, which is different due to the distinct settings of missing value; sd: standard deviation

Mediation association from birthweight to breast cancer mediated by age at menarche or age at menopause

Using the UK Biobank dataset, we aimed to explore the association between birthweight (the exposure X) and breast cancer (the outcome Y), with age at menarche (the first mediator M_1) and age at menopause (the second mediator M_2) as two potential mediators (Fig. 2). We implemented our mediation analysis under the traditional framework with varying covariates in different mediation models (21). The basic principle of incorporating covariates in these models was that we considered covariates if they were measured at the same time of collecting the outcome of focus. For example, when it came to age at menarche, we would not choose any covariates as none of them was measured at the age at menarche for a woman in the UK Biobank dataset; when it came to breast cancer, we considered BMI and smoking but would not include age at menopause if we only analyzed age at menarche. Moreover, we fit a linear model when analyzing continuous outcomes (e.g., age at menarche or age at menopause), whereas we fit a logistic model when analyzing binary outcomes (e.g., breast cancer).

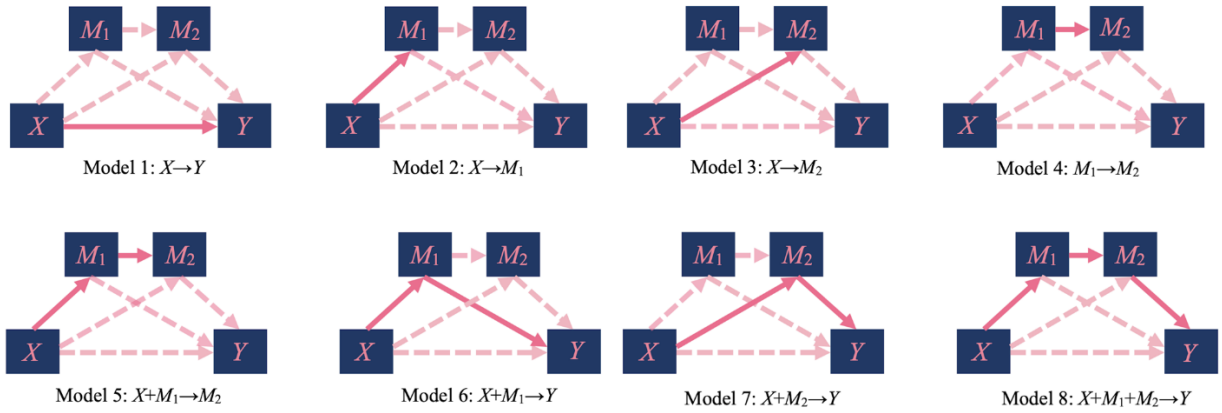

Fig. 2: Relationships between the exposure (X birthweight), the two mediators (M_1 age at menarche and M_2 age at menopause), and the outcome (Y breast cancer). Model 1 shows that Y can be affected by X without any mediators; Model 2 and Model 3 show the relationship between X and the two mediators; Model 4 describes the relationship between the two mediators; Model 5 shows the effect of X on M_2 with M_1 as an active mediator; Model 6 and Model 7 display the influence of X on Y when each of M_1 and M_2 acts as a promising mediator. Model 8 shows that the effect of X on Y is mediated by M_1 and M_2 in a sequential manner

With the two mediators under consideration, we here highlight that age at menarche can affect age at menopause but not vice versa (22). As a consequence, there are eight association possibilities, with four potentially consecutive paths from birthweight to breast cancer (Fig. 2): (i) a direct association between birthweight and breast cancer but not mediated by neither age at menarche nor age at menopause; (ii) birthweight affects breast cancer through age at menarche alone; (iii) birthweight impacts breast cancer through age at menopause alone; (iv) birthweight influences breast cancer through age at menarche, subsequently by age at menopause. The summation of effect sizes on these paths is equal to the total causal effect of birthweight on breast cancer, and the summation of the last three effect sizes can be viewed as the indirect effect of birthweight. Because the temporal ordering between these variables is determinative, these estimated effects have a causal interpretation if additional sequential ignorability assumptions are assumed satisfied (19).

Evaluating linear and non-linear relationship between birthweight and breast cancer

As would be shown below, though failing to detect an obvious linear relationship between birthweight and breast cancer in Model 1 and only identifying a marginally significant association between them in Model 8, we cannot completely exclude the likelihood that there might exist a non-linear association between birthweight and breast cancer (3, 9, 15). To assess such relationship, we performed a logistic regression by including the square of birthweight to examine its non-linear association with breast cancer. In addition, we also discretized birthweight into three categories (<2.5, 2.5~4.0, or >4.0 by following prior work) and carried out the similar logistic analysis above. Furthermore, we performed a stratification analysis in terms of the menopause status in each analysis setting. In the present work, all statistical analyses were implemented under the R software computing environment (23), with a significance level of 0.05.

Results

Mediation paths between birthweight and breast cancer

First, we implemented a logistic regression analysis to explore the linear effect of birthweight on breast cancer while adjusting for three available covariates (Model 1), but found a null association between them (P=0.230) (Table 2).

Second, we performed two separate linear regressions to study the association between birthweight and age at menarche (Model 2) or between birthweight and age at menopause (Model 3), and displayed that birthweight has a positive influence on each of two ages, with the effect size being β=0.041 (95% confidence intervals [CIs]: 0.025~0.057) for age at menarche and β=0.212 (95%CIs: 0.149~0.275) for age at menopause. At the same time, we found that age at menarche can positively affect age at menopause (Model 4), with the effect size being β=0.038 (95%CIs: 0.018~0.058).

Third, age at menarche can mediate the influence of birthweight on age at menopause (Model 5), with the effect size of age at menarche on age at menopause estimated to be β=0.045 (95%CIs: 0.020~0.070) conditional on birthweight; meanwhile, birthweight also has a direct effect on age at menopause (β=0.214, 95%CIs: 0.151~0.277). In addition, with age at menarche or age at menopause as a single mediator (Model 6 and Model 7), we discovered that both the two ages have a significantly negative impact on the risk of breast cancer, with odds ratio [OR]=0.95 (95%CIs: 0.92~0.97) for age at menarche and OR=0.96 (95%CIs: 0.95~0.97) for age at menopause, indicating the earlier the age at menarche or age at menopause, the higher the risk of breast cancer. However, in both mediation models, we did not detect the presence of direct effect of birthweight on breast cancer (P=0.205 and 0.096, respectively) after controlling for age at menarche or age at menopause.

Table 2: Potential mediation paths and effect sizes between birthweight and breast cancer with two mediators

	X→Y (Model 1) (case=3,376 and control=105,012) *β (se, P)*	***X→M₁ (Model 2) (n=106,811)*** *β (se, P)*	***X→M₂ (Model 3) (n=58,311)*** *β (se, P)*	***M₁→M₂ (Model 4) (n=93,768)*** *β (se, P)*
X	0.033 (0.027, 0.230)	0.041 (0.008, 6.42×10^{-8})	0.212 (0.032, 2.92×10^{-11})	
M_1				0.038 (0.010, 2.49×10^{-4})
M_2				
C_1	0.717 (0.039, 2.21×10^{-75})			
C_2	0.069 (0.035, 0.053)		-0.326 (0.042, 5.82×10^{-15})	-0.329 (0.033, 4.56×10^{-23})
C_3	0.004 (0.003, 0.206)			
	X+M₁→M₂ (Model 5) (n=57,514)	*X+M₁→Y (Model 6) (case=3,314 and control=102,948)*	*X+M₂→Y (Model 7) (case=2,274 and control=55,871)*	*X+M₁+M₂→Y (Model 8) (case=2,247 and control=55,102)*
	β (se, P)	*β (se, P)*	*β (se, P)*	*β (se, P)*
X	0.214 (0.032, 2.86×10^{-11})	0.035 (0.028, 0.205)	0.055 (0.033, 0.096)	0.061 (0.033, 0.067)
M_1	0.045 (0.013, 6.62×10^{-4})	-0.052 (0.011, 5.81×10^{-6})		-0.050 (0.014, 3.38×10^{-4})
M_2			-0.039 (0.004, 8.01×10^{-24})	-0.039 (0.004, 3.48×10^{-24})
C_1		0.708 (0.039, 3.50×10^{-72})		
C_2	-0.326 (0.042, 8.97×10^{-15})	0.079 (0.036, 0.028)	0.044 (0.043, 0.311)	0.056 (0.044, 0.199)
C_3		0.002 (0.003, 0.593)	0.005 (0.004, 0.268)	0.003 (0.004, 0.515)

Note: X: birthweight, M_1: age at menarche, M_2: menopausal age; C_1: menopause; C_2: smoke; C_3: BMI. The intercept is not included here

Finally, when incorporating age at menarche and age at menopause in the mediation model simultaneously (Model 8), we discovered that both the two ages are still significantly associated with breast cancer (OR=0.95, 95%CIs: 0.93~0.98 for age at menarche; OR=0.96, 95%CIs: 0.95~0.97 for age at menopause), and that birthweight has a positive effect on breast cancer at the marginally significant level (OR=1.06, 95%CIs: 1.00~1.13). To be more concise and evident, we demonstrated these estimated effects and relationships in Fig. 3.

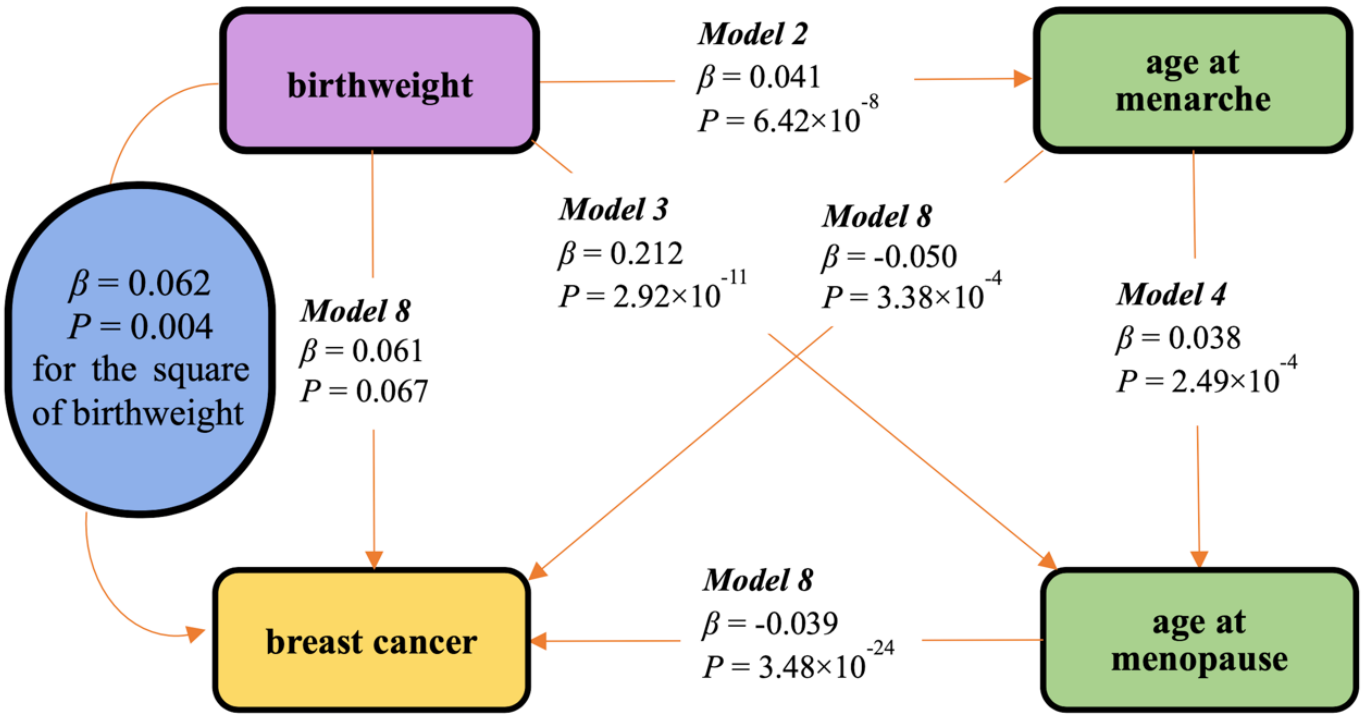

Fig. 3: Estimated effect sizes and the corresponding *P* values in the mediation models of birthweight and breast cancer. These solid lines represent the presence of significant associations or marginally significant associations

Non-linear relationship between birthweight and breast cancer

Though not detecting a linear relationship between birthweight and breast cancer in Model 1 (*P*=0.230) and only discovering a marginally significant association between them in Model 8 (*P*=0.067), there likely existed a non-linear association with breast cancer. To evaluate such relationship, we further performed a logistic regression by including the square of birthweight into models (Table 3). We observed a positive and significant association between the square of birthweight and breast cancer in terms of Model 1 (β=0.062, 95%CIs: 0.019~0.105), but such association becomes weaken and is no longer significant according to Model 8 (β=0.037, 95%CIs: -0.016~0.090). The stratification analysis in terms of the menopause status leads to the similar results in both models.

When incorporating discretized birthweight into the two models, we discovered that women birth with weight <2.5 or >4.0 have a higher risk of breast cancer in adulthood compared with those with normal birthweight (2.5~4.0) in both Model 1 and Model 8 (Table 3).

These above findings indicated that relationship between birth weight and breast cancer is curved in a U-shaped form. It varies in distinct age groups.

Table 3: Relationship between birthweight and breast cancer in Model 1 and Model 8 using continuous measurement of birthweight and discrete birthweight

	X→Y (Model 1) (case=3,376, control=105,012)	***X+M_1+M_2→Y (Model 8) (case=2,247, control=55,102)***		***X→Y (Model 1) case=3,376, control=105,012***	***X+M_1+M_2→Y (Model 8) case=2,247, control=55,102***
	Beta (se, P)	*Beta (se, P)*		*Beta (se, P)*	*Beta (se, P)*
X	-0.366 (0.141, 0.009)	-0.175 (0.176, 0.320)	X<2.5	0.037 (0.054, 0.494)	-0.092 (0.090, 0.305)
X^2	0.062 (0.022, 0.004)	0.037 (0.027, 0.173)	X>4	0.202 (0.053, 1.37×10^{-4})	0.225 (0.102, 0.027)
C_1	0.714 (0.039, 9.09×10^{-75})		C_1	0.713 (0.039, 1.46×10^{-74})	
C_2	0.068 (0.035, 0.054)	0.056 (0.044, 0.199)	C_2	0.067 (0.035, 0.057)	0.055 (0.044, 0.204)
C_3	0.004 (0.003, 0.292)	0.002 (0.004, 0.581)	C_3	0.004 (0.003, 0.273)	0.003 (0.004, 0.551)
M_1		-0.050 (0.014, 3.19×10^{-4})	M_1		-0.050 (0.014, 3.33×10^{-4})
M_2		-0.039 (0.004, 5.67×10^{-24})	M_2		-0.039 (0.004, 5.18×10^{-24})
C_1=0	*case=932, control=46,098*	*case=915, control=45,038*	C_1=0	*case=932, control=46,098*	*case=915, control=45,038*
X	-0.677 (0.253, 0.008)	-0.624 (0.261, 0.017)	X<2.5	0.183 (0.103, 0.076)	0.172 (0.104, 0.099)
X^2	0.109 (0.039, 0.006)	0.100 (0.040, 0.014)	X>4	0.238 (0.103, 0.021)	0.243 (0.104, 0.019)
C_2	0.043 (0.066, 0.519)	0.056 (0.067, 0.404)	C_2	0.045 (0.066, 0.497)	0.058 (0.067, 0.390)
C_3	0.001 (0.006, 0.870)	-0.003 (0.006, 0.673)	C_3	0.001 (0.006, 0.839)	-0.003 (0.006, 0.693)
M_1		-0.054 (0.021, 0.012)	M_1		-0.054 (0.021, 0.012)
C_1=1	*case=2,444, control=58,914*	*case=2,247, control=55,102*	C_1=1	*case=2,444, control=58,914*	*case=2,247, control=55,102*
X	-0.244 (0.168, 0.146)	-0.175 (0.176, 0.320)	X<2.5	-0.015 (0.064, 0.812)	-0.056 (0.067, 0.405)
X^2	0.044 (0.026, 0.085)	0.037 (0.027, 0.173)	X>4	0.189 (0.062, 0.002)	0.178 (0.065, 0.006)
C_2	0.078 (0.042, 0.062)	0.056 (0.044, 0.199)	C_2	0.076 (0.042, 0.068)	0.055 (0.044, 0.208)
C_3	0.005 (0.004, 0.205)	0.002 (0.004, 0.581)	C_3	0.005 (0.004, 0.246)	0.002 (0.004, 0.561)
M_1		-0.050 (0.014, 3.33×10^{-4})	M_1		-0.050 (0.014, 3.28×10^{-4})
M_2		-0.039 (0.004, 5.18×10^{-24})	M_2		-0.039 (0.004, 4.67×10^{-24})

Note: The left side shows the results obtained with continuous birthweight, while the right side shows results obtained with discretized birthweight. X: birthweight, M_1: age at menarche, M_2: menopausal age; C_1: menopause; C_2: smoke; C_3: BMI. The intercept is not included here

Discussion

A larger number of prior studies have demonstrated the existence of possibly positive association between birthweight and breast cancer; however, inconsistent, sometimes even controversial, findings still emerged. In the present we intended to handle this challenging problem. We offered implicit answers for some key questions regarding the association between the two traits. First, to examine whether the observed relationship represents a linear causality, we applied the logistic regression but did not identify a linear causal association between birthweight and breast cancer, which is in agreement with the null finding obtained from another study published recently (24). Second, to determine whether some growth traits and life processes may mediate the long-term impact of birthweight on breast cancer, we depended on the principle of mediation analysis (19, 20, 25, 26) and demonstrated that birthweight can indirectly influence breast cancer risk in adulthood via the path of age of menarche or age at menopause.

New contributions from our study

Compared with existing studies, the present work makes three new contributions to the relationship between birthweight and breast cancer. First, although it was implied by previous observations (3, 9, 15), there was no fully definitive conclusion regarding the non-linear association between the two traits. Here we explicitly revealed the existence of such non-linear association and showed that women birth with both low and high weight had higher risk to develop breast cancer in adulthood, reinforcing previous findings. However, the biological mechanisms underlying the association between birthweight and breast cancer are complex and have many possible explanations. For instance, birthweight is positively correlated with the estrogen level and the activity of the insulin-like growth factor-1 (IGF-1) level (13, 27); whereas both estrogen and IGF-1 are thought to have important effect on fetal growth and breast development (28); therefore, women with higher birthweight are more likely to develop breast cancer in later life (3, 29-32). Besides the impact of high concentration of pregnancy estrogen, the role of other pregnancy hormones or intrauterine factors in the observed relationship cannot be excluded (4, 10, 33).

Second, birth weight can indirectly influence breast cancer in adulthood via the path of age of menarche or age at menopause. The fetal environments and growths during childhood and adolescence are important for the development of breast cancer in adult life (9, 11). However, increased age at menopause had a protective influence on the development of breast cancer (β=-0.039 and P=3.48×10^{-24}). This finding was inconsistent with prior observations (34-36), which might be due to the biases by some unmeasured confounders (e.g., unreported oophorectomy). For instance, oophorectomy had an evidently protective effect against breast cancer risk in BRCA1 and BRCA2 carriers and there existed a substantial trend in reducing hazard with increasing time since oophorectomy (37).

Limitations

Our study is not without limitations. First, due to unavailability of many other early growth indicators (e.g., childhood obesity (12, 38)) in the UK Biobank cohort, we cannot further study their mediating role in the path from birthweight to adult breast cancer; therefore, the comprehensive causal path between them remains unclear. Second, like any retrospective studies, our observational analysis might be biased by confounding factors such as unknown/unmeasured covariates, information and recall bias, which can undermine the validity of our results. Third, we focused only on European population; extending to other ancestral groups to validate our conclusions is warranted in the future.

Conclusion

This study provided an in-depth insight into the observed relationship between birthweight and

breast cancer in later life, and revealed that non-linear impact and causal mediation commonly drive the connection between the two traits.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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