Association between born by caesarian section and anxiety, self-harm: a gene-environment interaction study using UK Biobank data

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Research Article

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Abstract

Background

Limited efforts have been paid to explore the underlying genetic mechanisms of born by caesarian section (CS) affecting the risks of adult anxiety and self-harm.

Methods

Using UK Biobank cohort, logistic regression model was first applied to evaluate the associations of adult anxiety and self-harm with born by CS. Using born by CS as exposure variables, genome-wide by environment interaction study (GWEIS) was then applied by PLINK2.0 to identify associated genes interacting with born by CS for anxiety and self-harm.

Results

In the observational study, significant associations were observed between born by CS and anxiety (odds ratio (OR) = 1.25; 95% confidence interval (CI), 1.13–1.37; $P = 1.19 \times 10^{-4}$), and self-harm (OR = 1.18; 95% CI, 1.07–1.29; $P = 3.62 \times 10^{-3}$). GWEIS revealed multiple significant gene interacted with born by CS at *P*-value $< 5.0 \times 10^{-8}$ for anxiety, such as DKK2 (rs13137764, $P = 1.24 \times 10^{-9}$) and ATXN1 (rs62389045, $P = 4.38 \times 10^{-8}$). For self-harm, significant gene-environment interactions of born by CS on self-harm were detected, such as ALDH1A2 (rs77828167, $P = 1.62 \times 10^{-8}$) and DAB1 (rs116124269, $P = 3.20 \times 10^{-8}$).

Conclusion

Our results suggested that born by CS was associated with the risk of adult anxiety and self-harm. We also discovered some genes interacted with born by CS might influence the risk of anxiety and self-harm, which may provide novel clues for the pathogenesis of those mental disorders.

Background

Mental disorder is a behavioral or mental pattern that causes significant distress or impairment of personal functioning [1]. Increasing incidence of mental illnesses places a heavy burden on global public health. According a recent study, the estimated global burden of mental illness accounts for 32.4% of years lived with disability (YLDs) and 13.0% of disability-adjusted life-years (DALYs) [2]. Anxiety and self-harm are two common but serious mental disorders. In a systematic review of prevalence studies across 44 countries, the global prevalence of anxiety disorders was estimated at 7.3% (95% CI 4.8–10.9), suggesting that one in 14 people around the world at any given time has an anxiety disorder [3]. According to the Global Burden of Disease study, anxiety disorders are the sixth leading cause of

disability in high-income and low-income countries, with the highest burden between age 15–34 years [4]. The World Health Organization estimates that, as of 2010, 880,000 deaths occur as a result of self-harm [5].

Previous studies demonstrated that genetic factors play an important role in the development of common mental disorders. For example, anxiety disorders are partly genetic, with twin studies suggesting 30–40% genetic influence on individual differences in anxiety [6]. A receptor gene for *BDNF* called *NTRK2* was associated with anxiety in a large genome-wide investigation [7]. In addition, twin and family studies indicated that non-suicidal self-harm is moderately heritable and identified shared genetic factors between self-harm and suicide, but the mechanism and extent underlying this genetic association still remain elusive [8, 9]. Pooley et al. studied six serotonergic gene polymorphisms in a well-characterized sample of 129 deliberate self-harm subjects and 329 comparison subjects and found that allelic variation in the TPH gene is a risk factor for deliberate self-harm [10]. However, the genetic mechanism of mental illness still remains elusive now.

The predominant view until now is that biological, psychological, environmental factors and their interactions all contribute to the development or progression of mental disorders [11]. Compared with previous approaches, by taking environmental factors into account, genome-wide by environment interaction study (GWEIS) is now becoming a popular method to explore disease associated genetic variations that interact with environmental risk factors. For example, by conducting a GWEIS, the researchers studied the interaction between genetic risk, psychotic symptoms and cannabis use and identified a SNP in the *P2RX7* gene which was associated with psychotic like experiences risk and cannabis use [12]. Aleix et al. performed a GWEIS of depressive symptoms and stressful life events in two UK population-based cohorts, two SNPs with genome-wide significant GxE effects were identified [13].

Caesarean section (CS) is the use of surgery to deliver babies. Reasons for this surgery may include obstructed labor, twin pregnancy, high blood pressure in the mother, breech birth, or problems with the placenta or umbilical cord [14]. Although CS surgery can reduce the mortality of mothers, fetuses and newborns to a certain extent, excessive selection of CS poses a threat to both short-term and long-term maternal and child health, such as increasing the risk of maternal uterine rupture and placental hyperplasia [15]. At the same time, offspring born by CS are prone to metabolic syndrome, immune and nervous system diseases [15]. Recently, the impact of CS on the neuro-psychological development of offspring has caused widespread concern. For example, in a systematic review and meta-analysis, the researchers showed that delivery by CS is associated with a modest increased odds of autism spectrum disorders and attention-deficit/hyperactivity disorder when compared to vaginal delivery [16]. Huang et al. suggested that children delivered by elective CS on maternal request have an increased risk to have emotional and behavioral problems prior to 39 gestational weeks at preschool age [17]. Based on previous study results, it is no hard to see that the way of delivery may have an impact on the neuro-psychological development of offspring.

In this study, we aimed to explore the effects of born by CS on adult anxiety and self-harm in UK Biobank cohort and further to investigate its underlying genetic mechanisms. First, we estimated the association of born by CS with the risk of anxiety and self-harm through a logistic regression model. GWEIS was then applied to explore the genetic variation interaction between born by CS and the risk of anxiety and self-harm. Our study holds potential for clarifying the functional relevance of C-section with adult anxiety and self-harm.

Materials And Methods

Ethical approval

UK Biobank has electronic signed consent from the study participants and ethical approval was obtained from Northwest Multi-Center Research Ethics Committee (reference 11/NW/0382).

UK Biobank dataset

The UK Biobank study is a large prospective cohort study included health, hospital-records and genetic data from 502,656 participants aged 40-69 in 2006 and 2010[18]. We used the imputed genotype dataset made available by UK Biobank in its July 2017 release. Subjects who had a self-reported gender inconsistent with the genetic gender, who were genotyped but not imputed or who withdraw their consents were removed. All participants agreed to use their anonymous data to conduct any health-related studies and to reconnect for further sub-studies.

Genotyping, quality control and imputation were performed by the UK Biobank. DNA samples of all participants in the UK Biobank were genotyped using either the Affymetrix UK BiLEVE (807,411 markers) or Affymetrix UK Biobank Axiom (825,927 markers) array[19]. SNPs were imputed by IMPUTE2 against the reference panel of the Haplotype Reference Consortium, 1000 Genomes and UK10K projects. Full details regarding these data are available elsewhere[20]. This research has been conducted using the UK Biobank Resource under Application Number 46478. The authors thank all UK Biobank participants and researchers who contributed or collected data.

Phenotypes definition

Born by CS was collected from the response to the UK Biobank on-line "Thoughts and Feelings" digestive health questionnaire: “Were you born by caesarian section?” by choosing “Do not know (-121)”, “No (0)”, “Yes (1)” and “Prefer not to answer (-818)”. The subjects whose answers are “Do not know (-121)” and “Prefer not to answer (-818)” were excluded in this study.

The case group criteria of anxiety were defined self-reported according to two UK Biobank fields: 20002 and 20544. Anxiety was selected based on the code 1287 from ID 20002 and code 15 from ID 20544 as cases. In order to obtain a comprehensive and accurate control group, we strictly set the control group threshold by Davis et al. research[21], which based on Patient Health Questionnaire (PHQ-9), general

anxiety disorder (GAD-7)[22]and another strict criterion based on composite international diagnostic interview short-form (CIDI-SF)[22, 23].

According to the previous study[24], self-harm phenotype was also defined using a touch screen questionnaire from UK Biobank. Participants were asked, “Have you deliberately harmed yourself, whether or not you meant to end your life?” and "Have you contemplated harming yourself (for example by cutting, biting, hitting yourself or taking an overdose)?". “Prefer not to answer” was set to “missing” in our analyses. Participants who answered both questions “NO” would be classified as the control group, and one or two “YES” would be classified as the case group (Full details in the Supplement information).

Observational analyses

The associations between born by CS and anxiety, self-harm behavior were estimated using a logistic regression model. The exposures variable was born by CS and the outcome variables were anxiety and self-harm. Sex, age and the first 10 principle components of population structure were adjusted as covariates. Beta coefficient with 95% confidence intervals (CI) and p-values were calculated by the logistic regression model. Allstatistical analyses were conducted by R 3.5.3 (https://www.r-project.org/).

Genome-wide by environmental interaction analysis

GWEISwas conducted to explorer the interaction between SNP and born by CS in mental disorders in UK Biobank cohort. The outcomes variables, including anxiety and self-harm behavior were adjusted by age, sex and the first 10 principle components of population structure. Based on the previous study, the genetic additive (ADD) model of PLINK2.0 was used in this study[25]. SNPs with call rate<0.95, Hardy Weinberg equilibrium testing P value < 0.001 and minor allele frequencies (MAFs) < 0.01 were excluded for variations quality-control[25]. A significant threshold was set at $P = 5.0 \times 10^{-8}$ for genome-wide by environment interaction effects. Circular Manhattan plots were generated using the “CMplot” R script (https://github.com/YinLiLin/R-CMplot).

Results

Basic characteristics of study samples

A total of 64,733 participants completed the anxiety related questions, and 11,852 were classified into case group, and the mean (SD) age was 54.9 (7.6) years old. A total of 75,334 participants answered the self-harm related questions, and 12,146 were classified into case group, and the mean (SD) age was 54.7 (7.7) years old (Table 1).

Association between born by CS and mental disorders

In UK Biobank cohort, significant associations were observed between born by CS and anxiety (odds ratio (OR) = 1.25, 95% confidence interval (CI), 1.13-1.37, $P = 1.19 \times 10^{-4}$), and self-harm (OR = 1.18, 95% CI, 1.07-1.29, $P = 3.62 \times 10^{-3}$) (Table 2).

GWEIS results

For anxiety, GWEIS identified multiple significant gene interacted with born by CS at *P*-value < 5.0×10^{-8}, such as DKK2 (rs13137764, P = 1.24×10^{-9}) and ATXN1 (rs62389045, P = 4.38×10^{-8}). For self-harm, several significant gene-environment interactions of born by CS on self-harm were detected, such as ALDH1A2 (rs77828167, P = 1.62×10^{-8}) and DAB1 (rs116124269, P = 3.20×10^{-8}) (Figure 1, Table 3).

Discussion

In this study, we conducted an observational and GWEIS analysis to explore the relationship between born by CS and adult anxiety and self-harm. We found significant associations between born by CS and the risk of anxiety and self-harm respectively. In addition, GWEIS identified multiple genes interacted with born by CS for anxiety and self-harm.

It has been suggested by a previous systematic review and meta-analysis that birth by cesarean delivery is associated with certain neurodevelopmental and psychiatric disorders. For example, the researchers have shown that delivery by CS is associated with a modest increased odds of autism spectrum disorders and attention-deficit/hyperactivity disorder when compared to vaginal delivery[16]. According to a Swedish population-based cohort, elective CS is associated with an increase in offspring psychosis[26]. In a longitudinal study of Australian children, Polidano et al. observed a negative relation between cesarean birth and a range of cognitive outcomes measured from ages 4 to 9[27]. However, there is no study focus on the risk of born by CS on adult anxiety and self-harm. Our study identified significant associations between born by CS and its risk on anxiety and self-harm in UK Biobank cohort, suggesting an important role of born by CS in affecting anxiety and self-harm in adults.

Our GWEIS also revealed several candidate genetic variants interacting with born by CS for anxiety, such as DKK2 and ANTX1. DKK2 is an important member of the DKK gene family. The DKK gene family is an ancient and evolutionarily conserved gene family[28]. In recent years, a large number of studies showed that DKK gene family plays an important role in embryonic development, neural regeneration, synaptogenesis and so on[29]. Therefore, its role in neuropsychiatric disorders, such as cognitive impairment and emotional disorder, has attracted increasing attention[29]. According to a previous study, DKK2 converges on β-catenin using distinct transduction pathways required to activate Wnt/β-catenin signaling and induce neural crest cells[30]. Zhao et al. have demonstrated an anxiety-specific response and contribution of activated neural stem cells to chronic pain through Wnt/β-catenin signaling, which may be targeted for treating chronic pain- or other diseases-associated anxiety[31]. However, there is few studies about the effect of DKK2 on anxiety. We found DKK2 interacting with born by CS for anxiety. Further in vivo and in vitro functional studies are needed on this effect.

Ataxin-1 (ATXN1), the gene mutated in spinocerebellar ataxia type 1 (SCA1), is another significant candidate genetic variants interacting with born by CS for anxiety. Lu et al. performed a series of behavioral tests on the ATXN1–with its paralog ataxin 1–like (ATXN1L) conditional knockout mouse

lines to assess general activity, anxiety, learning and memory, and social behavior[32]. In the elevated plus-maze test, conditional knockout mice spent more time in the open arm and less time in the closed arm than control mice which was possibly as a result of reduced anxiety[32]. According to a previous study which modeled early-life unpredictable stress in developing rats and found enhanced levels of anxiety when tested in adulthood compared to control, non-stressed adult rats[33]. The results showed that these behavioral changes were associated with upregulated ANTX1 gene within the amygdala[33].

For self-harm, GWEIS also identified several candidate genetic variants interacting with born by CS, such as ALDH1A2 and DAB1. According to a previous study, after nonfatal self-harm, adolescents and young adults were at markedly elevated risk of suicide[34]. It has been reported that self-harm and suicide are predominant causes of decreased survival in patients suffering from schizophrenia[35]. ALDH1A2, encodes an enzyme for astrocyte-derived retinoic acid, is a key neuronal morphogen with relevance for schizophrenia. For example, Wan et al. observed a positive association between ALDH1A2 and schizophrenics in the Chinese population[36]. In a methylome-wide association study of schizophrenia, ALDH1A2 was identified to be the second-most significant site[37]. DAB1, a key component of the Reelin pathway[38], is sufficient to induce behavioral deficits related to psychiatric disorders. A recent study revealed that DAB1 conditional knockout mice showed hyperactivity, decreased anxiety-like behavior, and deficit in spatial reference and working memory[39]. The results indicated that the Reelin-DAB1 signaling in the cortex can be an important molecular basis for the regulation of the behaviors[39]. Teixeira et al. observed a causal relation between the downregulation of DAB1 protein levels during development and the structural and behavioral deficits associated with psychiatric diseases in the adult[40].

In contrast with GWAS, GWEIS discovered some novel genes that might influence the risk of anxiety and self-harm. Previous studies focused on the genetic effect on mental disorders, less study have assessed the interaction role of gene and environment on the mechanism of these complex diseases. Our study demonstrated the interaction association between born by CS and anxiety, self-harm. As far as we known, this is the first systemic study exploring the effect of born by CS as environmental factor on mental disorders for adults. Our study holds great potential for clarifying the functional relevance of born by CS with mental disorders and provide novel clues for the pathogenesis of those mental disorders.

However, some limitations of this study should be noted. First, like GWAS, some significant SNPs found by GWEIS are located in non-coding region, which still pose challenges for us to better illustrate our results. Second, all subjects in this study are from European ancestry. Therefore, it should be careful to apply our study results to other ethnic groups. Furthermore, although several genes have been reported to have interaction effects with born by CS, further experimental studies are needed to validate its specific biological functions and mechanisms.

In summary, we observed significant association between born by CS and the risk of adult anxiety and self-harm using UK Biobank cohort. GWEIS analysis identified multiple candidate genes which may serve as the underlying genetic mechanisms of the observed association. Further studies are expected to validate our findings and clarify the potential mechanism of identified gene-environment interaction.

Declarations

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Author contributions

YJ, SC and FZ conceived and designed the study, and wrote the manuscript, YJ, SC and FZ collected the data and carried out the statistical analyses, YW, JY, LL, BC, CL, XC, YY and OK made preparations for the manuscript at first. All authors reviewed and approved the final manuscript.

Availability of data and materials

The data are available upon request from the first author.

Ethical approval and consent to participate

UK Biobank has electronic signed consent from the study participants and ethical approval was obtained from Northwest Multi-Center Research Ethics Committee (reference 11/NW/0382).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Basic Characteristics of study samples from UK Biobank

		Born by caesarean section
Anxiety	Case/Control	11,852/52,881
	Sex (Female)	41,082
	Age (SD)	54.93(7.61)
Self-harm	Case/Control	12,146/63,188
	Sex (Female)	48,652
	Age (SD)	54.71(7.66)

* Age was described as Mean ± standard deviation.

Table 2. Association between anxiety, self-harm behavior and born by caesarean section

Instrument	Outcome	β	SE	T	P value	OR (95% CI)
Born by CS	Anxiety	0.22	0.06	3.85	0.0001	1.25 (1.13-1.37)
	Self-harm	0.16	0.06	2.91	0.0036	1.18 (1.07-1.29)

Note: CS, caesarean section, SE, standard error, T, t-test, CI, confidence interval, OR, odd ratios.

Table 3. Summary of gene-environment interaction analysis between SNP and born by CS for anxiety and self-harm

	CHR	Gene	Model	P value
Anxiety	4	DKK2	ADD × born by CS	1.24×10^{-9}
	10	DIP2C	ADD × born by CS	1.06×10^{-8}
	8	COL22A1	ADD × born by CS	1.39×10^{-8}
	6	ATXN1	ADD × born by CS	4.38×10^{-8}
Self-harm	2	LRRFIP1	ADD × born by CS	6.02×10^{-10}
	15	ANPEP	ADD × born by CS	1.31×10^{-8}
	15	ALDH1A2	ADD × born by CS	1.62×10^{-8}
	1	DAB1	ADD × born by CS	3.20×10^{-8}
	22	CELSR1	ADD × born by CS	4.03×10^{-8}
	18	COLEC12	ADD × born by CS	4.45×10^{-8}

Figures

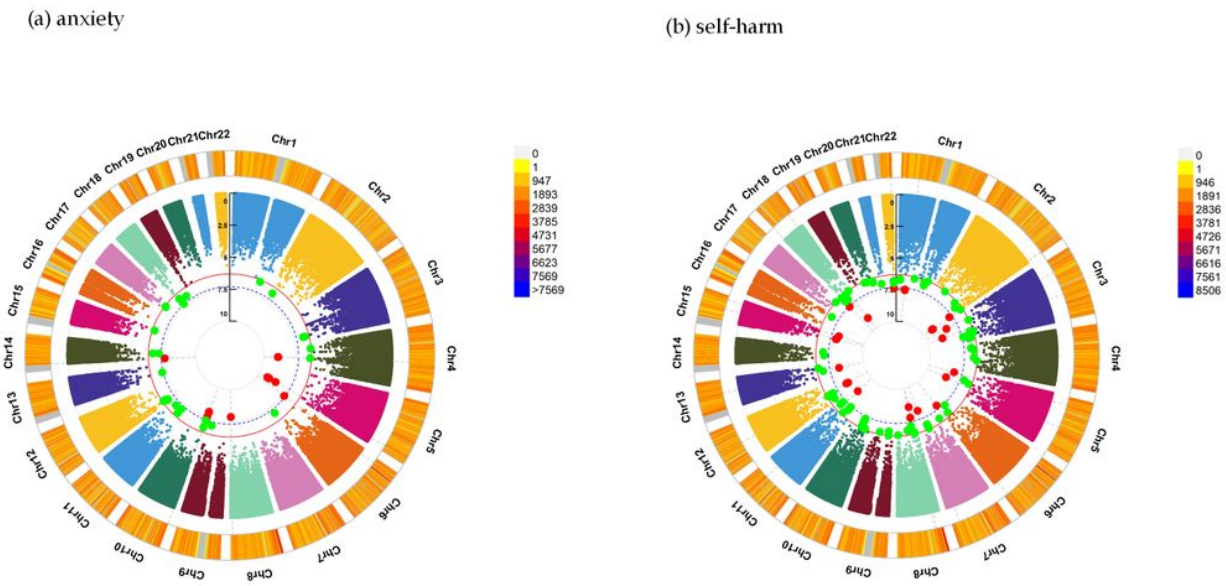

Figure 1

Chromosomal regions interacting with born by caesarean section for anxiety (a) and self-harm (b).

*From the center, the circos depicts the $-\log_{10}$ P-values of each variant. Red plots represent the P value < 5×10^{-8} and green plots represent P value < 5×10^{-7}. The plots were generated using the “CMplot” R script (https://github.com/YinLiLin/R-CMplot).

Supplementary Files

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