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## **Depression in Swedish Women: Relationship to Factors at Birth**

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**Abstract** Depression is a common and serious disorder that may have developmental origins. Birth-related factors have been related to childhood and adult occurrence of somatic as well as psychiatric disorders, but studies on the relationship between birth-related factors and depression are few and show mixed results. In addition, varying methods have been used to assess depression. Standardized clinical criteria to diagnose depression, combined with birth data collected from midwife records have not been used in most studies. **Participants in the Prospective Population Study of Women in Sweden (803 women), born 1914, 1918, 1922 and 1930, provide information on birth factors and depression. Women participated from 1968 at mid-life ages of 38-60 years, to 2000, when they were age 78-92 years.** Original birth records containing birth weight, length, head circumference, and gestational time, as well as social factors were obtained. Lifetime depression was diagnosed via multiple information sources. Symptoms were assessed using the Comprehensive Psychopathological Rating Scale and diagnoses were based on DSM-III-R criteria. Over their lifetime, 44.6% of women in this sample experienced depression. Birth weights  $\leq 3500$  grams [odds ratio (OR), **age-adjusted**=1.72; 95% CI 1.29-2.28,  $P<0.001$ ] and shorter gestational time (OR, **age-adjusted**=1.13; 95% CI 1.04-1.24,  $P=0.005$ ) were independently associated with a higher odds of lifetime depression in a logistic regression model **adjusted for age**. Lower than median birth weights and shorter gestational time were related to lifetime depression in women. Both neurodevelopmental and environmental contributions to lifetime depression may be considered.

**Keywords** Depression, birth factors, birth weight, gestational age, population-based, women

## **Introduction**

**The fetal origins, or Barker hypothesis, was first described by Barker and Osmond in 1986 [1] and proposes that somatic diseases occurring during adult life, such as coronary heart disease, type 2 diabetes, stroke and hypertension originate in developmental plasticity, are responses to undernutrition during fetal life and infancy [2]. Evidence accumulates for a fetal origin of psychiatric disorders, as well [3-4]. Historically, birth weight, birth length, head circumference, and gestational time have been common birth parameters measured to better understand potential developmental influences of the central nervous system. Birth weight represents accumulation of adipose tissue during fetal development, which has been shown to contribute to short- and long-term health [5]. The importance of fetal fat accumulation is illustrated by the observation that premature babies are at higher risk of slower neurological development and smaller brain size [6]. Thus, birth weight has been deemed an important marker of neurodevelopment.**

Since depression is a common and multifactorial disorder that is episodic over the life course, and often leads to serious consequences such as increased mortality and suicide, [7] it is of great importance to identify early factors that may be related to its occurrence and etiology.

Epidemiological studies are valuable to evaluate this question.

Several studies show an association between lower birth weight and later depression, [4, 8-10] while others find no such relationship [11-12]. Few report on both birth weight and gestational time. Among those that do, two found an association for shorter gestational time, [13-14] and

another supported the finding on lower birth weight [15]. Independent effects of both factors in relationship to depression have not been reported. Most of these studies measure depression at one point in time and focus on younger populations.

We had the opportunity to investigate birth-related factors including birth weight, gestational time, birth length, and head circumference, in relationship to lifetime depression evaluated on multiple occasions using several different sources of information, in a sample of women observed longitudinally **over 32 years from mid- to late-life**. These women were enrolled in the Prospective Population Study of Women (PPSW) in Gothenburg, Sweden.

## **Methods**

### **Subjects**

PPSW began in 1968-69 with a baseline examination of 1381 women (90.6% participation rate) [16] born in 1914, 1918, 1922 and 1930, who originated from a representative sample obtained from the Revenue Office Register in Gothenburg. Of these women, 1140 participated in at least one psychiatric examination, and for 803 of them birth factor information, retrieved from original midwife records in the 1990's, was available. Participants were re-examined over the next 32 years in 1974, 1980, 1992, and 2000. Informed consent was obtained from all participants and/or their relatives. The study was approved by the Ethics Committee for Medical Research of University of Gothenburg.

**A comparison of women with versus without birth factor information in the 1968 baseline sample showed that women with birth factor information were younger in 1968 compared**

to those without (45.6 (5.8) versus 46.8 (5.3) years,  $p < 0.001$ ), however there was no difference in level of education obtained in adult life (OR 1.21 95% CI 0.96, 1.53,  $p = 0.113$ ).

### **Birth-related factors**

Birth-related factors were abstracted from original midwife records as previously described [17]. Biological birth-related factors that were recorded include birth weight, gestational time, birth length, and head circumference. While information on birth weight and gestational time were routinely recorded for all birth cohorts studied, birth length was first recorded in Swedish midwife records in 1917, and head circumference in 1926. Additional information was collected when available, including parental social group (categorized in five class levels based on occupation of the father, or if missing or no father, on the mother), maternal age, maternal parity and the participant's birth location (i.e., home vs. hospital) and twin status [17].

### **Psychiatric examination**

Psychiatric examinations were performed by psychiatrists in 1968, 1974, 1980, and 1992 and by psychiatric nurses in 2000. **Beginning in 1987**, the diagnosis of depression was made using criteria described in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised (DSM-III-R) [18], **and also retrospectively for examinations in 1968, 1974 and 1980**. Application of these criteria was based on the psychiatric examinations, history of previous depression as evaluated by a clinical psychiatrist [19,20], and depression between examinations, information from medical records and the Swedish Hospital Discharge Registry. At the psychiatric examinations, the Comprehensive Psychopathological Rating Scale (CPRS) [21] was used to rate psychiatric symptoms and signs at face-to-face examinations. Medical records were collected from hospitals and outpatient departments including psychiatric and primary care in

Gothenburg. The Swedish Hospital Discharge Registry provided diagnostic information for individuals discharged from hospitals since 1978. Lifetime depression included major depressive disorder, dysthymia, and depression not otherwise specified. A diagnosis of dysthymia was made without the two year criterion as information on symptom duration was not specified [22].

### **Statistical analyses**

Birth weights were available for all 803 participants; however birth record information was incomplete for other birth-related factors. Gestational time was available for 750, birth length for 648, and head circumference for 444 women. Only values within acceptable ranges were used. All values for birth weight, birth length, and head circumference fulfilled this criterion. However, due to some extreme outliers for gestational time, only individuals with gestational times ranging 1.5 standard deviations from the mean of 40 weeks (between 35.2 – 44.9 weeks) (n=715) were included in analyses with gestational time. Varying sample sizes are **represented** across analyses due to the varying completeness of birth factor information. **Birth weight, gestational time, birth length, and head circumference were normally distributed.**

Means and standard deviations were calculated for all continuous variables, and t-tests were used to assess mean differences by depression status. Continuous measures of birth factors were used in all initial analyses, and further analyses were conducted considering birth weight, birth length, and head circumference in quintiles and as dichotomous variables using median values as cut-offs. Birth weight was considered as a continuous variable in 500 gram increments. Pearson correlation coefficients were calculated for all continuous variables. Partial correlation coefficients were calculated after **adjustment for age**. Linear trends in means of birth factors across level of social group were also tested. Due to inaccuracies in estimating date of depression onset, logistic regression analyses were used to estimate the odds of lifetime depression by birth-

related factors, both biological and social. **Age-adjusted** birth-related factors that were significant at a level of  $P < 0.05$ , were subsequently included in multivariate models. Cox proportional hazards analyses were run to estimate the relationship between birth factors and overall mortality. Results were considered statistically significant at  $P < 0.05$ . SPSS, version 15.0 was used to analyze study data.

## Results

Over their lifetime, 44.6% of women in this sample experienced depression. Their average birth parameters are shown in table 1. Evaluating interrelationships among birth-related factors showed that birth weight was associated with a variety of other factors. Higher maternal age (Pearson's partial  $r$ , cohort adjusted = 0.135,  $df=799$ ,  $P < 0.001$ ) and maternal parity (Pearson's partial  $r$ , cohort adjusted = 0.253,  $df=800$ ,  $P < 0.001$ ) were related to a higher birth weight. Increasing level of parental social group was related to higher birth weight ( $P$  for trend = 0.032). Babies born at home (observed among 37.1 %) were heavier (mean (SD)=3562 (559) vs 3482 (558) grams, **age-adjusted**  $P=0.049$ ), and being one of a twin pair (observed among 2.1%) was associated with a lower mean birth weight (mean (SD)=2707 (519) vs 3529 (548), **age-adjusted**  $P < 0.001$ ) and a shorter gestational time (mean (SD)=38.5 (2.2) vs 40.1 (1.7), **age-adjusted**  $P=0.001$ ) than being a non-twin. As expected, birth-related factors were correlated with each other (range of **age-adjusted** Pearson's partial  $r=0.210-0.694$ ,  $df=416$ ).

Overall, lower average birth weight and shorter gestational time were related to lifetime depression (table 2). Further analyses showed that birth weights of 3500 grams or less (3500 grams was the median and approximate mean of the sample), and shorter gestational time were

independently associated with higher odds of lifetime depression (table 3). **Dose-response relationships were not observed.** There were no differences between women with and without lifetime depression regarding other biological birth-related factors including birth length and head circumference. Birth-related factors were not related to overall mortality (data not shown).

(Table 1 here)

(Table 2 here)

(Table 3 here)

As expected, individuals below the median birth weight had shorter mean gestational time compared to those with birth weight above the median (39.9 (1.8) vs 40.4 (1.6) weeks,  $P < 0.001$ ). The direction of the relationship between gestational time and lifetime depression did not differ by median birth weight strata. Among those with a birth weight greater than the median, shorter gestational time was related to lifetime depression (OR 1.23, 95% CI 1.06-1.43,  $P = 0.006$ ). However, there was no evidence of an interaction between birth weight and gestational time in a logistic regression model.

## Discussion

To our knowledge, this study is the first to show independent associations between both birth weight and gestational time and a lifetime diagnosis of depression. This study supports previously observed associations between lower birth weight [4, 8-10,15] or shorter gestational time [13-14] and higher occurrence of depression. However this is the first to report independent effects of both of these birth factors in the same sample.

**Our reported prevalence of lifetime depression is supported by other studies [23-25]. Some studies report lower prevalences of lifetime depression but these studies are often retrospective and do not include elderly populations [23]. It has been suggested that lifetime prevalence of mental disorders may be twice as high in prospective versus retrospective studies [26]. Our group reported a comparable incidence of depression in adults age 70 years and older [25].**

Important strengths of this epidemiological investigation is that it includes: 1) a representative and well characterized population sample; 2) birth data that were abstracted from original midwife records, which are more accurate than self-report [27]; 3) rigorous standardized criteria for diagnosing clinical psychiatric disorders; 4) depression ascertained over more than 32 years of observation and based on multiple sources of information; and 5) independent collection of birth factor information and psychiatric endpoints, thus reducing systematic bias. Finally, there was consideration for several potential confounding factors including maternal age, maternal parity, parental social group, birth location, and twin status.

Differences in results obtained from epidemiological studies evaluating birth factors in relationship to mental disorders may be due to a variety of factors. Not all studies have all birth parameters, birth data are of varying quality, and criteria used to diagnose depression vary. To our knowledge we are one of the only studies to have a life time diagnosis of depression in addition to it being based on clinical DSM-III-R criteria.

**Possible etiological mechanisms**

The developmental origins hypothesis, simply described, is the influence of early life environment on structural and functional development during critical periods, which may lead to short- and long-term consequences for the individual, even later disease [2]. In relationship to depression, lower birth weight and shorter gestational time may be related to glucocorticoid-induced programming of the hypothalamic-pituitary-adrenal (HPA) axis. In addition, low birth weight has been associated with higher plasma cortisol concentrations in adults [28] and elevated cortisol has been related to depression in adults [29].

Another potential link between birth weight, gestational time, and depression is related to adipose tissue. Birth weight is, in part, a marker of adipose tissue stored in the fetus, especially during later development when grams of fetal body fat double between 35 and 40 weeks of gestation [30]. Fetal fat accumulation has long been known to be important for the brain, as premature babies are at higher risk of slower neurological development [6]. Adipose tissue is an important energy source, a source of bioactive free fatty acids, and is also the largest endocrine organ in the human body [30]. Additional biological candidate mechanisms that relate birth weight and gestational time to depression may be related to other hypothalamic-pituitary-end organ axes, such as the hypothalamic-pituitary-thyroid (HPT), [31] and –gonadal (HPG) [32] axes.

Maternal factors during pregnancy may also be related to lower birth weight, shorter gestational time and depression symptoms in the offspring. Some of these factors include external stress, smoking, psychiatric illness, preeclampsia, SES, and maternal birth weight [33]. Some of these factors are available in this study, but we did not have the power to investigate them.

One may suspect that the serious outcomes associated with lower birth weights are related to severe intrauterine growth retardation and pathologically low birth weights. However, our results regarding birth weights of 3500 grams or less, are in line with two other studies. One showed that women weighing less than 3000 grams at birth had an increased risk of depression later on, in early adulthood [9]; and another showed that participants with birth weights less than 2500 g had an increased risk of major depression compared to those weighing more than 3500g [4].

Processes traditionally associated with pathologically low birth weights and preterm births occur over a continuum, and thus variation within the normal range may confer some degree of susceptibility to developing depression later in life. Lower birth weight and shorter gestational time could cause less neuroplasticity [34] from birth in these women, thus be markers of a low tolerance or susceptibility state for depression.

As with all research studies, there are limitations. First, all members of the sample are female, White, and living in Sweden, thereby limiting sex, racial, and cultural generalizability. However the concurrence of our findings with other birth cohort studies is encouraging. Second, the sample size is small compared to other developmental origins study cohorts. However, our rigorously collected exposure and outcomes data and long follow-up time fill a niche in the developmental origins cohort literature. **Third, gestational time is estimated based on date of last menstrual period. Given the socioeconomic and nutritional conditions during the early twentieth century, leading to more prevalent amenorrhea and dysmenorrhea, as well as lack of birth control leading to rapidly occurring consecutive births, the dates for this parameter may have been imprecise.** However this is one of the methods still used today; and we reduced the influence of potential outliers by including only individuals with gestational times ranging 1.5 standard deviations from the mean. Fourth, depression is an episodic disorder.

Despite the use of case records, registry data and retrospective information to complement depression diagnoses via psychiatric examinations over a 32 year period, there are most likely cases of depression in the non-depressed group. **Fifth, a limited number of confounders are available for consideration in these analyses, making it difficult to tease out the relative contribution of potentially etiological factors. The potential for residual confounding is obvious, and something that cannot be overcome given the historical nature of the birth factors data. We are using birth factors data attained via secondary data collection efforts more than 70 years after they were originally recorded. These data are not typically available in population-based studies of adults, and are strengths of this dataset. Even so, there are many unknowns related to maternal and paternal exposures, fetal development, and post-natal development. These factors are beyond the scope of this paper.** Finally, history of previous depression prior to the baseline examination in 1968 may be subject to recall bias, and was not ascertained in the structured fashion that was employed during the observation period that followed. However, if we excluded these women from the analyses, results were similar in all essential aspects, although not statistically significant due to a reduction in power. In conclusion, lower weight at birth and shorter gestational time were related to lifetime depression in women, which suggests a neurodevelopmental etiology of depression.

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### **Ethical approval**

The study was approved by the Ethics Committee for Medical Research of University of Gothenburg.

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**Table 1** Birth cohort and birth-related factors in 803 participants in the Prospective Population Study of Women

<b>Birth Cohort</b>		
	<i>N</i> (%)	
1914	89 (11.1)	
1918	200 (24.9)	
1922	257 (32.0)	
1930	257 (32.0)	
<b>Birth-related Factors*</b>		
	Mean (SD)	Range
Weight, grams	3511.5 (559.6)	1600.0-5500.0
Gestational time, weeks**	40.1 (1.7)	35.3-44.9
Length, cm	50.2 (2.7)	35.0-64.0
Head circumference, cm	34.8 (1.7)	24.0-40.0

\*  $n=803$  with information on birth weight, 715 with gestational time, 648 with length, and 444 with head circumference

\*\* Gestational time within 1.5 SDs was used, thus included are those greater than 35.2 and less than 44.9 weeks

**Table 2** Birth-related factors in women with versus without lifetime depression

	<b>No Depression</b>		<b>No Depression</b>		<i>t</i>	<i>P-value</i>	<b>Age-adjusted <i>P-value</i></b>
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)			
<b>Birth-related Factors*</b>							
Weight, grams	445	3552.2 (555.7)	358	3460.9 (561.0)	2.3	0.021	0.025
Gestational time, weeks**	393	40.3 (1.6)	322	39.9 (1.8)	2.9	0.004	0.005
Length, cm	360	50.3 (2.7)	288	50.1 (2.7)	1.2	0.218	0.353
Head circumference, cm	256	34.8 (1.7)	188	34.8 (1.7)	-0.3	0.728	0.518

\*  $n=803$  with information on birth weight, 715 with gestational time, 648 with length, and 444 with head circumference

\*\* Gestational time within 1.5 SDs was used, thus included are those greater than 35.2 and less than 44.9 weeks.

**Table 3** Odds of lifetime depression in a population sample of women by birth-related factors, adjusted for birth cohort

	OR (95% CI)	Age-adjusted <i>P-value</i>
<b>Birth-Related Factors</b>		
<i>Univariate Models</i>		
<b>Biological Factors*</b>		
Birth weight $\leq$ 3500, grams	1.72 (1.29-2.28)	<0.001
Shorter gestational time, weeks	1.13 (1.04-1.24)	0.005
Birth length, cm	0.97 (0.92-1.03)	0.353
Head circumference, cm	0.96 (0.86-1.08)	0.518
Being a twin	1.74 (0.65-4.66)	0.268
<b>Social Factors**</b>		
Maternal age, years	0.99 (0.97-1.02)	0.568
Maternal parity, number of live births	0.98 (0.93-1.04)	0.565
Increasing parental social group	0.97 (0.86-1.09)	0.570
Birth location, home <i>versus</i> hospital	0.96 (0.72-1.28)	0.779
<b>Multivariate Model***</b>		
Birth weight $\leq$ 3500, grams	1.63 (1.20-2.22)	0.002
Gestational time, weeks	1.11 (1.01-1.22)	0.018

\*  $n=803$  with information on birth weight, 715 with gestational time, 648 with length, 444 with head circumference, and 803 with twin status

\*\*  $n=802$  with information on maternal age, 803 with maternal parity, 797 with parental social group, and 803 with birth location

\*\*\*Multivariate model based on factors significant at  $P<0.05$ , birth weight and gestational time, in cohort-adjusted analyses,  $n=715$