ORIGINAL ARTICLE

Depression in Young Adults With Very Low Birth Weight

The Helsinki Study of Very Low-Birth-Weight Adults

Katri Räikkönen, PhD; Anu-Katriina Pesonen, PhD; Kati Heinonen, PhD; Eero Kajantie, MD, PhD; Petteri Hovi, MD; Anna-Liisa Järvenpää, MD, PhD; Johan G. Eriksson, MD, PhD; Sture Andersson, MD, PhD

Context: Little is known about the mental health outcomes of very low-birth-weight (VLBW) (<1500 g) infants in young adulthood.

Objective: To test whether young adults aged 18 to 27 years with VLBW differ from term control subjects in depressive symptoms, current use of antidepressant medication, and the rate of depression diagnosed by a physician.

Design: Retrospective longitudinal study.

Setting: Academic research.

Participants: A total of 162 VLBW young adults (response rate, 65.1%) and 172 term control subjects (response rate, 54.8%) born between February 22, 1978, and November 8, 1985, in Helsinki, Finland.

Main Outcome Measures: Antidepressant use, history of physician-diagnosed depression, Beck Depression Inventory score, and Center for Epidemiologic Studies Depression Scale score.

Results: The VLBW participants reported 20.1% (95% confidence interval [CI], –40.8% to –5.1%) lower CES-D scores than the controls (P=.02). However, this finding was confined to 110 VLBW participants who were born appropriate for gestational age (birth weight ≥–2 SDs according to Finnish birth weight charts), whose Center for Epidemiologic Studies Depression Scale scores were 29.1% (95% CI, –53.7% to –8.4%) lower than those of the controls (P=.004). Furthermore, VLBW participants born appropriate for gestational age were 4.8 (95% CI, 1.3-10.0) times less likely to report a depression diagnosis than controls (P=.02). In contrast, 52 VLBW participants born small for gestational age (birth weight <–2 SDs according to Finnish birth weight charts) reported 36.2% (95% CI, 1.1%-83.5%) higher Beck Depression Inventory scores (P=.04), were 4.0 (95% CI, 1.1-14.3) times more likely to use antidepressants (P=.03), and were 2.5 (95% CI, 1.0-6.3) times more likely to report a depression diagnosis (P=.04) compared with controls.

Conclusions: This is the first study (to our knowledge) to show that intrauterine growth pattern may modify associations between VLBW and depression. Intrauterine growth retardation rather than VLBW per se may pose a risk of depression in young adulthood.

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Author Affiliations: Departments of Psychology (Drs Räikkönen, Pesonen, and Heinonen) and Public Health (Dr Eriksson) and Institute of Clinical Medicine and Hospital for Children and Adolescents (Drs Kajantie, Hovi, Järvenpää, and Andersson), University of Helsinki; and Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute (Drs Kajantie, Hovi, and Eriksson); Helsinki, Finland.

INTRODUCTION OF MODERN METHods of neonatal intensive care in the past few decades has resulted in improvements in survival and in decreases in rates of neurosensory and neuromotor impairments of preterm infants with very low birth weight (VLBW) (<1500 g).[1,2] However, studies of long-term outcomes of VLBW infants have indicated problems in mental health, psychological development, and social and academic competencies in childhood[3] and adolescence.[4] Accumulating evidence suggests that these problems may persist into young adulthood. Young adults with VLBW score lower on intelligence[5-7] and academic achievement[3] tests, report less satisfactory school performance and ability to learn and concentrate,[8] and are less frequently enrolled in or graduate from high school[5] than control subjects born at term.

Relative to the data on cognitive and academic achievements, data on mental health outcomes of VLBW young adults are scanty and inconsistent. Cooke[1] found no differences between subjects aged 19 to 22 years with VLBW and term control subjects in self-reported anxiety, depression, or overall mental health. Also, Bjerager et al[8] found no differences between subjects aged 18 to 20 years with VLBW and term control subjects in self-reported mental health. Hack et al[7] found that (relative to term control subjects) 20-year-old subjects with VLBW were characterized by a lower level of self-reported delinquent behavior but had higher levels of parent-reported thought and attention problems and withdrawn and anxious-depressed behaviors; in addition,

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women with VLBW were characterized by more self-reported internalizing behaviors. Apart from these data on VLBW young adults, other data are more consistent in demonstrating that subjects with low birth weight (LBW) (≤2500 g) are prone to experiencing depressive symptoms[9-12] and to receiving a clinical diagnosis of depression[13] at various points in life compared with those with birth weights greater than 2500 g.

In the present study, we tested whether young adults aged 18 to 27 years with VLBW differ from term control subjects in depressive symptoms, current use of antidepressant medication, and the rate of depression diagnosed by a physician. Findings from a few studies[7,14,15] suggest that intrauterine growth patterns reflected in being born small for gestational age (SGA) and appropriate for gestational age (AGA) may modify the developmental outcomes of VLBW infants. Therefore, we also tested whether VLBW young adults born AGA and SGA differ from term controls and from each other in depressive symptoms, current use of antidepressants, and rate of depression diagnosis. Finally, we tested whether common pregnancy-related risk factors such as maternal smoking and preeclampsia are related to the outcome measures.

METHODS

PARTICIPANTS

The original study cohort consisted of 474 consecutive VLBW infants born between February 22, 1978, and November 8, 1985, in one of several maternity hospitals that serve the geographic area of the province of Uusimaa, Finland. Of these, 335 (70.7%) were discharged alive from the neonatal intensive care unit of the Children's Hospital at the Helsinki University Central Hospital, the only tertiary neonatal care center in the province of Uusimaa. Of those discharged alive and those who died, 238 (71.7%) and 94 (28.3%), respectively, were born AGA (birth weight ≥−2 SDs according to Finnish birth weight charts),[16] and 97 (68.3%) and 45 (31.7%), respectively, were born SGA (birth weight <−2 SDs according to Finnish birth weight charts). The neonatal mortality rates of infants born AGA and SGA were not statistically significantly different (χ^2_1=0.55, P=.49).

We selected control subjects from the records of all consecutive births of the hospitals. For each VLBW survivor, we included the next available singleton infant who was of the same sex, born at term (gestational age, ≥37 weeks), and not SGA as a control subject. We then traced these individuals in the Population Register Center as young adults. Mortality rates from hospital discharge to June 20, 2004, were 1.8% for young adults with VLBW and 1.0% for term controls; we were able to trace 95.1% and 96.8%, respectively, of the survivors. We invited 255 young adults with VLBW and 314 controls who were living in the greater Helsinki area, and 166 (65.1% [43.3% men]) young adults with VLBW and 172 (54.8% [40.6% men]) controls agreed to participate in the study as previously described.[17] Of 166 VLBW participants, 162 had valid data on the main outcome measures; 2 participants did not fill out the depressive symptom scales embedded in a psychological survey, and 2 additional participants had attended special education for the developmentally delayed during school age and were excluded.

As previously described by Hovi et al,[17] participants in this study and nonparticipants were similar in birth weight, standardized birth weight, gestational age, maternal preeclampsia, days of mechanical ventilation, days of oxygen, and discharge age, except that the rate of cerebral palsy at 15 months of age was lower among the VLBW participants (10 subjects [6.0%]) than among the VLBW nonparticipants (17 subjects [19.1%]) (P=.005). The study protocol was approved by the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at the Helsinki University Central Hospital, and all participants gave their written informed consent. The perinatal data were derived from maternal welfare clinic and hospital records; parental, participants' developmental, and young adult characteristics were measured at a clinical examination.[17]

MAIN OUTCOME MEASURES

In conjunction with the clinical visit,[17] participants' depressive symptoms were assessed using questionnaires, and they were asked whether they used antidepressant medication currently and if they had been diagnosed by a physician as having depression. The Beck Depression Inventory (BDI)[18] and the Center for Epidemiologic Studies Depression Scale (CES-D)[19] were used to measure the severity and frequency of depressive symptoms. In addition to considering the BDI and CES-D scores as continuous measures, we used the predefined and validated cut point scores of 10, 19, and 30 for defining those at risk of mild, moderate, and severe depression, respectively, according to the BDI,[18] as well as a cut point score of 16 for defining those at risk of moderate-severe depression according to the CES-D.[19] The internal reliability coefficient (Cronbach α) was .91 for the BDI and for the CES-D.

Sixteen participants reported that they were currently taking antidepressants. Ten were taking serotonin reuptake inhibitors, 4 were taking noradrenaline-serotonin reuptake inhibitors, 1 was taking tricyclic antidepressants, and 1 was taking an unnamed antidepressant. Thirty-four participants reported a past diagnosis of depression.

STATISTICAL ANALYSIS

As the primary data analytic tools, we used multiple linear regression analysis (depressive symptoms as continuous measures) and logistic regression analysis (categories of depressive symptoms [with those reporting no symptoms as a reference group], current use of antidepressants, and depression diagnosis). We examined differences in the main outcome measures between (1) VLBW young adults and term controls, (2) VLBW young adults born AGA and term controls, and (3) VLBW young adults born SGA and term controls, in addition to (4) differences within the VLBW group between those born AGA and those born SGA. Because women, older individuals, those with cognitive problems, those in lower socioeconomic groups, and those with higher body mass index (BMI) have been shown to demonstrate greater preponderance to depression,[11] and because BMI gain is among the adverse effects of some antidepressants (eg, some noradrenaline-serotonin reuptake inhibitors that our study participants reported using), the group comparisons were conducted with the following covariates in the models: sex, age, parental level of education, BMI (calculated as weight in kilograms divided by height in meters squared), and attendance at a modified curriculum during school age (as a proxy of cognitive problems). The BDI and CES-D scores were logarithmically transformed to attain normality. Group differences are reported in percentages and in odds ratios with 95% confidence intervals (CIs).

RESULTS

CHARACTERISTICS OF THE SAMPLE

Table 1 gives the birth weight, gestational age, and other perinatal, parental, and adult characteristics in the VLBW group (162 subjects [93 women and 69 men], catego-

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Table 1. Characteristics of Very Low-Birth-Weight (VLBW) Infants Born Appropriate for Gestational Age (AGA) and Small for Gestational Age (SGA) and of Term Control Subjects[a]

Characteristic	VLBW AGA (n=110)	VLBW SGA (n=52)	Control (n=172)	*P* Value: Control vs VLBW	*P* Value: Control vs VLBW AGA	*P* Value: Control vs VLBW SGA	*P* Value: VLBW AGA vs VLBW SGA
Perinatal							
Birth weight, g							
Boys	1151 (209)	1079 (228)	3632 (471)	<.001	<.001	<.001	.21
Girls	1122 (214)	1125 (240)	3567 (471)	<.001	<.001	<.001	.95
Standardized birth weight							
Boys	−0.4 (0.9)	−2.9 (0.7)	0.0 (1.0)	<.001	.02	<.001	<.001
Girls	−0.4 (0.9)	−3.2 (0.8)	0.1 (1.0)	<.001	.005	<.001	<.001
Gestational age, wk							
Boys	28.2 (1.6)	30.6 (1.5)	39.9 (1.2)	<.001	<.001	<.001	<.001
Girls	28.2 (1.6)	31.7 (2.1)	40.3 (1.1)	<.001	<.001	<.001	<.001
Multiple birth, twin or triplet	17 (15.5)	9 (17.3)	0	<.001	<.001	<.001	.76
Cerebral palsy	10 (9.1)	3 (5.8)	0	<.001	<.001	.002	.47
Developmental delay	1 (0.9)	1 (1.9)	0	.14	.21	.07	.59
Modified curriculum	4 (3.6)	3 (5.8)	0	.006	.01	.002	.53
Preeclampsia	12 (10.9)	22 (42.3)	13 (7.6)	<.001	.33	<.001	<.001
Maternal smoking during pregnancy[b]	20 (19.6)	10 (20.0)	28 (16.7)	.48	.54	.59	.95
Parental							
Highest education of either parent[c]							
Elementary	13 (11.8)	4 (7.8)	11 (6.4)				
High school	25 (22.7)	17 (33.3)	31 (18.1)				
Intermediate	43 (39.1)	14 (27.5)	56 (32.7)				
University	29 (26.4)	16 (31.4)	73 (42.7)	.03	.03	.12	.30
Adult							
Age, y	22.5 (2.1)	22.2 (2.1)	22.5 (2.2)	.73	.95	.39	.38
Height, cm							
Men	174.6 (8.1)	174.8 (7.3)	180.6 (6.4)	<.001	<.001	<.001	.93
Women	163.3 (8.2)	160.0 (6.1)	167.4 (6.8)	<.001	<.001	<.001	.05
Body mass index[d]							
Men	21.5 (3.2)	23.7 (4.2)	23.3 (3.2)	.04	.002	.71	.02
Women	22.8 (4.0)	20.8 (2.9)	22.8 (3.7)	.24	.95	.008	.02

[a] Data are given as mean (SD) or as number (percentage). *P* values refer to group comparisons conducted using univariate analysis of variance with continuous measures and using Pearson product moment correlation χ^2 test with categorical measures. Data are missing in the VLBW and control groups.
[b] Data are missing on 10 subjects in the VLBW group and on 4 subjects in the control groups.
[c] Data are missing on 1 participant each in the VLBW and control groups.
[d] Calculated as weight in kilograms divided by height in meters squared.

rized as 110 born AGA [62 women and 48 men] and 52 born SGA [31 women and 21 men]) and in the term control group (172 subjects [103 women and 69 men]). In addition to differing from term control subjects, VLBW young adults born SGA compared with those born AGA were more frequently born to mothers with preeclampsia ($P<.001$). Further comparisons within the VLBW group showed that, compared with their VLBW counterparts born AGA, VLBW women born SGA were on average 3.3 cm shorter ($P=.05$) and had a 2.0 lower BMI in young adulthood ($P=.02$), while VLBW men born SGA had a 2.2 higher BMI in young adulthood ($P=.02$). There were no other statistically significant differences between the VLBW young adults born AGA and SGA.

ASSOCIATIONS BETWEEN COVARIATES AND DEPRESSION

Next, we examined the associations between the covariates and depression in the VLBW and control groups. Compared with men, women in the VLBW and control groups scored 64.0% and 33.6% higher, respectively, on the CES-D and 116.2% and 40.5% higher, respectively, on the BDI ($P<.01$ for all). Among the VLBW group, current use of antidepressants was reported by 9 women (5 born SGA and 4 born AGA) and by no men ($P=.008$), while among the control group current use of antidepressants was reported by 2 women and by 5 men ($P=.08$). Diagnosis of depression was reported by 13 women (mean [SD] age at onset, 19.6 [2.8] years; age range, 13-25 years) and by no men ($P=.001$) among the VLBW group but by 14 women and by 7 men among the control group ($P=.48$).

We also tested whether the other covariates were associated with depression. After controlling for sex, VLBW young adults who had attended a modified curriculum reported lower CES-D and BDI scores ($P<.03$ for both), while none reported current use of antidepressants or a depression diagnosis. Among VLBW women, higher BMI was related to a greater likelihood of use of antidepressants ($P=.06$). In the control group, after controlling for

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Table 2. Depressive Symptoms Among Young Adults With Very Low Birth Weight (VLBW) and Among Term Control Subjects[a]

Variable	Center for Epidemiological Studies Depression Scale Score		Beck Depression Inventory Score		Current Use of Antidepressants		Diagnosis of Depression	
	Difference in %	*P* Value	Difference in %	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value
VLBW vs control	−20.1 (−40.8 to −5.1)	.02	2.0 (−20.9 to 25.7)	.85	1.9 (0.7 to 5.5)	.22	0.7 (0.4 to 1.6)	.44
VLBW AGA vs control	−29.1 (−53.7 to −8.4)	.004	−11.6 (−40.4 to 12.8)	.34	1.2 (0.3 to 4.2)	.83	0.2 (0.1 to 0.8)[b]	.02
VLBW SGA vs control	2.2 (−28.3 to 22.9)	.85	36.2 (1.1 to 83.5)	.04	4.0 (1.1 to 14.3)	.03	2.5 (1.0 to 6.3)	.04
VLBW SGA vs VLBW AGA	25.2 (−0.1 to 58.3)	.06	50.4 (12.2 to 101.6)	.007	7.3 (1.2 to 45.3)	.03	18.4 (3.3 to 103.0)	.001

Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age.
[a] Data are given as value (95% confidence interval) and refer to group comparisons in multiple linear and logistic regression analyses after adjusting for sex, age, parental educational attainment, body mass index in young adulthood, and attendance at a modified curriculum during school age.
[b] Corresponds to 4.8 (95% confidence interval, 1.3-10.0) times lower risk.

sex, higher BMI in adulthood was related to higher BDI scores (P=.04), and older age was related to greater likelihood of reporting a depression diagnosis (P=.04). There were no other statistically significant associations between the covariates and depression in the VLBW and control groups.

Finally, we tested whether the depressive outcome measures were interrelated in the VLBW and control groups. All the associations were in the expected direction and were statistically significant ($P<.001$ for all).

DIFFERENCES BETWEEN VLBW YOUNG ADULTS AND TERM CONTROL SUBJECTS IN DEPRESSION

As summarized in **Table 2**, after controlling for sex, age, parental education, BMI in young adulthood, and attendance at a modified curriculum, participants in the VLBW group reported 20.1% lower CES-D scores than the controls (P=.02). Seventeen percent (n=27) of VLBW young adults and 25.0% (n=43) of term controls were at increased risk of moderate-severe depression according to the CES-D (odds ratio, 0.6; 95% CI, 0.3-1.0; P=.06). The groups did not differ in BDI scores. Twelve percent (20 subjects [16, 3, and 1 of mild, moderate, and severe categories, respectively]) of VLBW participants and 15.1% (26 subjects [15, 8, and 3 of mild, moderate, and severe categories, respectively]) of term controls were at increased risk of mild-severe depression according to the BDI scores (odds ratio, 0.8; 95% CI, 0.4-1.5; P=.46). The VLBW participants and control subjects did not differ from each other in their current use of antidepressants or in their rate of depression diagnosis.

Next, we tested whether VLBW young adults born AGA and those born SGA differed from term control subjects in depressive symptoms. As summarized in Table 2, after adjusting for the covariates, the VLBW participants born AGA reported 29.1% lower CES-D scores than the control subjects (P=.004). **Figure 1** shows that their risk of moderate-severe depression according to the CES-D scores was 2.6 (95% CI, 1.3-5.6) times lower than that of the term controls (P=.009). The VLBW participants born AGA were also 4.8 (95% CI, 1.3-10.0) times less likely to report a depression diagnosis than the control subjects (P=.02) (Table 2 and **Figure 2**).

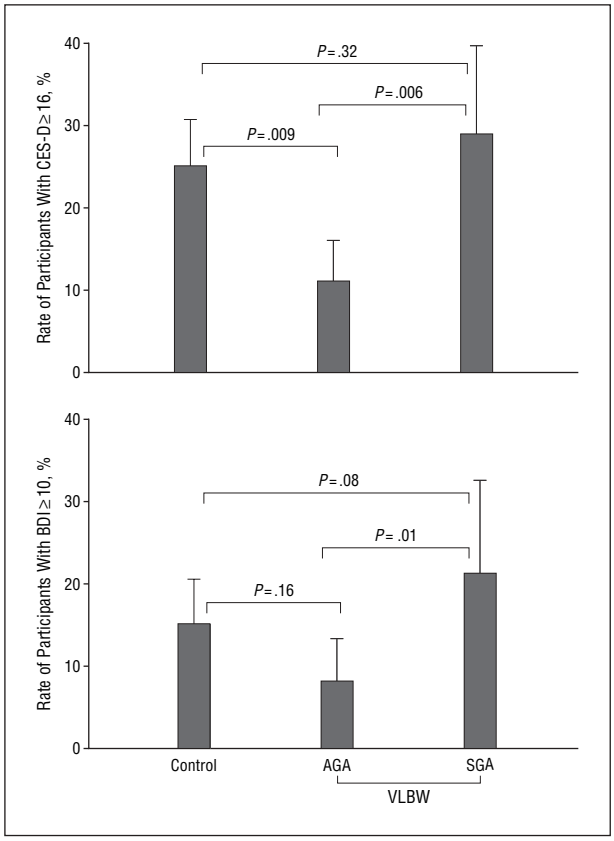

Figure 1. Rates of very low-birth-weight (VLBW) young adults born appropriate for gestational age (AGA) and small for gestational age (SGA) and of term control subjects at risk of moderate-severe depression according to the Center for Epidemiological Studies Depression Scale (CES-D ≥16) and at risk of mild-moderate depression according to the Beck Depression Inventory (BDI ≥10). Error bars refer to 95% confidence intervals, and *P* values refer to group comparisons after adjusting for sex, age, parental educational attainment, body mass index in young adulthood, and attendance at a modified curriculum during school age.

In contrast, the VLBW participants born SGA reported 36.2% higher BDI scores than the control subjects (P=.04) (Table 2). Figure 1 shows that their risk of mild-severe depression according to the BDI scores was 2.1 (95% CI, 0.9-4.9) times greater than that of the control subjects (P=.08). Furthermore, the VLBW participants born SGA were 4.0 times more likely to report current antidepressant use (P=.03) and 2.5 times more likely

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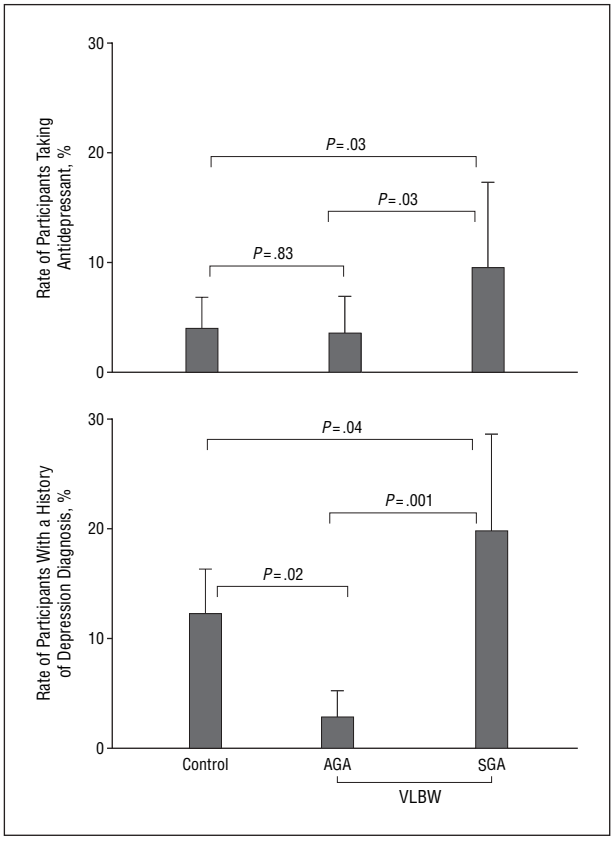

Figure 2. Rates of very low-birth-weight (VLBW) young adults born appropriate for gestational age (AGA) and small for gestational age (SGA) and of term control subjects using antidepressants and reporting a depression diagnosis. Error bars refer to 95% confidence intervals, and *P* values refer to group comparisons after adjusting for sex, age, parental educational attainment, body mass index in young adulthood, and attendance at a modified curriculum during school age.

to report a depression diagnosis (P=.04) compared with the control subjects (Table 2 and Figure 2).

DIFFERENCES BETWEEN VLBW YOUNG ADULTS BORN AGA AND SGA IN DEPRESSION AND OTHER PERINATAL RISKS

After adjustments for the major covariates, comparisons between the VLBW young adults born AGA and SGA in depressive symptoms showed that those born SGA had 25.2% higher CES-D scores (P=.06) and 50.4% higher BDI scores (P=.007) than those born AGA (Table 2). Figure 1 shows that the risk of VLBW young adults born SGA for moderate-severe depression according to the CES-D scores was 3.8 (95% CI, 1.5-9.5) times greater (P=.006) and for mild-severe depression according to the BDI scores was 3.7 (95% CI, 1.3-10.4) times greater P=.01) compared with the risk of VLBW young adults born AGA. Furthermore, VLBW young adults born SGA were 7.3 times more likely to report current antidepressant use (P=.03) and 18.4 times more likely to report a depression diagnosis (P=.001) compared with those born AGA (Table 2 and Figure 2).

Maternal smoking during pregnancy was associated with higher BDI scores (32.5% [95% CI, 0.0%-74.5%] for offspring of smokers, (P=.05), independent of VLBW and the other covariates, but not with CES-D scores, antidepressant use, or depression diagnosis ($P>.35$ for all). Maternal preeclampsia was not statistically significantly associated with depression ($P>.68$). We then reran all the analyses contrasting VLBW participants with term controls, VLBW AGA and SGA participants with term controls, and against each other, with maternal smoking during pregnancy and preeclampsia as additional covariates. The statistically significant associations remained so ($P<.05$ for all).

The associations remained statistically significant ($P<.05$ for all) after excluding from the analyses 13 subjects with cerebral palsy and 2 subjects with mild developmental delay (despite reporting a diagnosis of developmental delay, both had attended a standard school curriculum at age-appropriate school grades and were retained in the previously described analyses). Those with and without these impairments did not differ from each other in depressive symptoms ($P>.31$), and none of those with impairments reported using antidepressants currently or having a depression diagnosis. In the VLBW group, twins and triplets did not differ from singletons in depressive symptoms ($P>.33$ for both), and adjustment for multiple pregnancy had no effect on our results.

Finally, we tested whether differences in depressive symptoms between the groups varied by sex but found no evidence for sex interaction ($P>.25$ for all interaction terms). Tests for sex interaction in the analyses of antidepressant use and depression diagnosis were not feasible, as these were reported by women only. However, when we restricted these analyses to women, the associations remained statistically significant ($P<.05$ for all).

COMMENT

We found that young adults with VLBW reported less depression in young adulthood than term control subjects. However, this was strongly dependent on intrauterine growth pattern of the VLBW participants: those born AGA reported fewer depressive symptoms and were less likely to report a depression diagnosis than term controls, while those born SGA reported more depressive symptoms, used antidepressants more frequently, and were more likely to report a depression diagnosis than term controls. Furthermore, not only did the VLBW participants differ from their term counterparts in depressive symptoms but also, when those born AGA and SGA were contrasted with each other, those born SGA reported more depression. We found no evidence that sex, age, maternal preeclampsia, BMI in young adulthood, parental educational attainment, maternal smoking during pregnancy, and attendance at a modified curriculum during school age explained the findings. The results did not change when participants with cerebral palsy or mild developmental delay were excluded from the analyses.

These findings are in disagreement with earlier findings on mental health outcomes of VLBW young adults, as no studies (to our knowledge) have indicated that VLBW young adults born AGA would fare better than their counterparts born SGA or at term. Two studies[1,8] found no differences between young adults with VLBW and term control subjects in self-reported mental health, including depression. A third study[7] found less self-reported delin-

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quent behavior among VLBW women and men, more self-reported internalizing problem behavior among VLBW women, and a range of other problem behaviors among VLBW women and men as indicated by their parents. There are methodological differences between the present study and these previous studies such as measurements used, mental health outcomes, informants (self vs parents), diversity in ethnic backgrounds, and sample differences in the range of birth year and age at testing. However, inferences on the extent to which these differences account for the discrepant findings cannot be made. To our knowledge, ours is the first study to report that mental health outcomes of VLBW participants may be dependent on intrauterine growth pattern.

However, our findings parallel some of earlier findings that suggest that the developmental outcomes of VLBW infants may be modulated by AGA and SGA status. Hack et al[7] noted that the parent-reported greater inattention that characterized VLBW young adults leveled off when VLBW infants born SGA were removed from the analyses. However, other problem behaviors characterizing VLBW young adults' self-reports or parent-reports were unaffected by AGA or SGA status. A recent study[14] of VLBW adolescents indicated that SGA status was the best predictor of parent-reported behavior problems that characterized VLBW adolescents. Furthermore, a small but growing number of findings regarding SGA and AGA infants' cognitive development suggest that VLBW infants born SGA may fare worse during the course of development than those born AGA.[15]

Our findings also parallel recent findings among preterm adults. Preterm 31-year-old adults who weighed less than 1900 g at birth and whose standardized birth weight (–0.4 SD according to birth weight charts) is comparable to that of the VLBW AGA group in our study reported fewer depressive symptoms and experienced psychiatric disorders less frequently than term control subjects.[20] Finally, our findings also parallel those among cohorts not restricted to participants born preterm.[9-13] These findings demonstrate that adolescents and adults with LBW report increased rates of depressive symptoms and more frequently have a depression diagnosis. Studies[9,11-13,21] in which gestational age at birth has been available show that these associations are attributable to slow fetal growth rather than solely to prematurity. Therefore, our findings add to the literature by underlining the importance of differentiating VLBW infants born AGA from those born SGA. The results also suggest that intrauterine growth retardation, as reflected in SGA status, rather than VLBW per se may pose a risk of depression later in life.

Although the mechanisms of these associations are unknown, intrauterine glucocorticoid programming of the hypothalamic-pituitary-adrenal axis (HPAA) has been proposed as a key candidate mechanism.[22,23] Findings in animals have linked reduced activity of the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (which protects the fetus from excess maternal cortisol) with intrauterine growth restriction and with increased HPAA activity and anxiety like behaviors.[24] In humans, preterm[25,26] and term[26] SGA births have been associated with reduced activity of this placental enzyme. Small size at preterm[27] and term[28] birth is also linked with altered HPAA activity, which in turn is among the key biologic characteristics of depression. Obviously, the HPAA is coupled with many other hormonal systems, including the growth hormone–insulin–like growth factor system, which is a key regulator of growth and brain development[29] and may be involved in the pathogenesis of depression.[30]

Genetic mechanisms also cannot be overlooked. There is evidence that depression and depressive symptoms are at least moderately heritable.[31] Maternal distress during pregnancy may be associated with shorter length of gestation[32] and with less optimal development of the offspring.[33] Findings from a recent study[9] of young adults with LBW suggest that the association between LBW and depression is not explained by maternal depression-anxiety during pregnancy, but we had no parental history of depression available in our study and cannot resolve the question of confounding by parental depression.

Although an obvious explanation of the findings of less depression among AGA infants compared with SGA infants is their more optimal development until delivery, we have no ready explanation of why AGA infants scored lower in depressive symptoms than term control subjects. We can only speculate that if the physiologic stress regulatory systems of the AGA infants compared with the SGA infants are less affected in utero,[26] making them physiologically less vulnerable to stress-related adversities, perhaps their risk is further decreased by their lower threshold to stress and to depression-inducing environments: VLBW young adults are prone to less risk taking and delinquent adulthood compared with term control subjects.[7,8] Parenting may have a role in buffering the risk further.[2,34]

Limitations of our study include the absence of data available on mental health outcomes during the course of development until young adulthood, such that we cannot detect continuity and change in behaviors in the VLBW and control groups over time. Because we do not have parent-reports available, comparison with previous findings relating to these outcomes cannot be made. However, there are no parent versions available for the CES-D and BDI that we used. Our study cohort included few participants who used antidepressants and reported a depression diagnosis, these being confined to women in the VLBW group, restricting assessment of the external validity and reproducibility of the findings. Furthermore, premature infants today and infants of our cohort may differ. Survival has improved, and breakthroughs in therapy have changed the character of some diseases.[35] Although our original cohort comprised the entire population of VLBW infants in the area who were discharged alive after neonatal intensive care, our participants may not be representative of the original cohort. Furthermore, 65.1% of the VLBW young adults and 54.8% of the control subjects participated, introducing a potential bias toward healthier participants.[36] Our results are based on internal comparisons within the study sample, and nonparticipation would introduce bias only if the effect of VLBW on young adult outcomes in nonparticipants differed.

We conclude that VLBW is associated with fewer self-reported depressive symptoms in young adulthood. However, this finding was confined to the VLBW young adults

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born AGA, who were also less likely to report a depression diagnosis. The VLBW young adults born SGA reported more depressive symptoms, used antidepressants more frequently, and were more likely to report a depression diagnosis than the term control subjects. Therefore, intrauterine growth retardation rather than VLBW per se may pose a risk of depression in young adulthood.

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Correspondence: Katri Räikkönen, PhD, Department of Psychology, University of Helsinki, PO Box 9, FI-00014 Helsinki, Finland (katri.raikkonen@helsinki.fi).
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