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Maternal early pregnancy body mass index and diurnal salivary cortisol in young adult offspring

Satu M Kumpulainen[a,*], Kati Heinonen[a], Nina Kaseva[b], Sture Andersson[c], Aulikki Lano[c], Rebecca M Reynolds[d], Dieter Wolke[e], Eero Kajantie[b,c,f,g], Johan G Eriksson[b,h,i], Katri Räikkönen[a]

[a] Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland
[b] National Institute for Health and Welfare, Helsinki, Finland
[c] Children's Hospital, Helsinki University Hospital and University of Helsinki, Finland
[d] University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
[e] Department of Psychology, University of Warwick, UK
[f] National Institute for Health and Welfare, Oulu, Finland
[g] PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Finland
[h] Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Finland
[i] Folkhälsan Research Center, Helsinki, Finland

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ABSTRACT

Background Maternal early pregnancy overweight (body mass index [BMI] 25.0–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) are associated with mental and physical health adversities in the offspring. Prenatal programming of the hypothalamic-pituitary-adrenal (HPA) axis has been put forward as one of the mechanisms that may play pathophysiological role. However, evidence linking maternal overweight and obesity with offspring HPA-axis activity is scarce. We studied if maternal early pregnancy BMI is associated with diurnal salivary cortisol, a marker of HPA-axis activity, in young adult offspring.

Methods At a mean age of 25.3 (*standard deviation [SD]* = 0.6) years, 653 Arvo Ylppö Longitudinal Study participants collected saliva samples for cortisol analyses, at awakening, 15 and 30 min thereafter, 10:30AM, 12:00PM, 5:30PM and at bedtime. Maternal BMI was calculated from weight and height verified by a measurement in the first antenatal clinic visit before 12 weeks of gestation derived from healthcare records.

Results Per each one kg/m^2 higher maternal early pregnancy BMI offspring diurnal average salivary cortisol was -1.4% (*95% CI*:-2.6, -0.2, p_{FDR} = 0.033) lower, at awakening it was -2.4% (*95% CI*:-4.0, -0.7, p_{FDR} = 0.025) lower and the morning average salivary cortisol was -2.0% (*95% CI*:-3.4, -0.5, p_{FDR} = 0.017) lower. These associations were independent of the offspring's own young adulthood BMI, and other important covariates.

Conclusion Our findings show that young adult offspring born to mothers with higher early pregnancy BMI show lower average levels of diurnal cortisol, especially in the morning. Whether these findings reflect prenatal programming of the offspring HPA-axis activity warrants further investigation.

1. Introduction

In 2014, 14.9% of adult women worldwide were obese (body mass index [BMI] ≥30 kg/m^2) (NCD-RisC, 2016) with the global prevalence of obesity in women expected to increase to 21% by 2025 (NCD-RisC, 2016). Consequently, the prevalence of obesity in pregnant women has been increasing varying from 7 to 21% across European Union countries (Devlieger et al., 2016; Euro-Peristat, 2013) and 18 to 31% across the United States (Branum et al., 2016; Deputy et al., 2018). The number of pregnant women who are overweight (BMI 25–29.99 kg/m^2) is high as well:17-28% in European union countries (Euro-Peristat, 2013) and 23–28% in the United States (Deputy et al., 2018). Overweight and obesity in pregnancy pose multiple health risks for the mother, increasing risk for gestational diabetes (Torloni et al., 2009), hypertensive pregnancy disorders (Gaillard et al., 2011; Wang et al., 2013), pregnancy and postpartum depression (Kumpulainen et al., 2018; Molyneaux et al., 2014), and longer hospital stays after delivery (Chu et al., 2008). Maternal overweight and obesity also increase the risk of caesarean section delivery (Poobalan et al., 2009) and adverse neonatal outcome, including preterm birth (McDonald et al., 2010),

* Corresponding author at: Department of Psychology and Logopedics, P.O. Box 21, 00014 University of Helsinki, Helsinki, Finland.
E-mail address: satu.m.kumpulainen@helsinki.fi (S.M. Kumpulainen).

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large-for-gestational-age birth weight and macrosomia (Ehrenberg et al., 2004), birth injury, asphyxia and respiratory problems, convulsions, hypoglycaemia (Blomberg, 2013) and congenital malformations (Persson et al., 2017). Maternal overweight and obesity are also major risk factors for stillbirth (Flenady et al., 2011).

The adverse consequences of maternal overweight and obesity on the offspring not only pertain to the neonatal and infancy periods, but emerging evidence suggests that they may persist into later life stages. In follow-up studies, the adverse outcomes associated with maternal early pregnancy overweight and obesity include increased risk of asthma and wheezing in children (Forno et al., 2014), poorer cardiometabolic profile (higher BMI, fat mass, blood pressure, lipids, inflammation) in children and adults (Eriksson et al., 2015; Godfrey et al., 2017; Kaseva et al., 2018), higher risk of neurodevelopmental delay (Girchenko et al., 2018) and poorer neurocognitive functioning in children (Álvarez-Bueno et al., 2017; Contu and Hawkes, 2017; Huang et al., 2014), and higher risk of any mental and psychological development (Kong et al., 2018; Rivera et al., 2015), attention deficit hyperactivity (Gardner et al., 2015; Kong et al., 2018; Rodriguez, 2010; Rodriguez et al., 2008), conduct (Kong et al., 2018), mood (Kong et al., 2018; Van Lieshout et al., 2013), anxiety (Rivera et al., 2015), and autism spectrum disorders (Gardner et al., 2015; Kong et al., 2018; Xiang et al., 2015) in children, psychosis in children (Kong et al., 2018) and schizophrenia in adults (Khandaker et al., 2012). The adverse adult outcomes additionally include increased risk for diabetes (Eriksson et al., 2014; Godfrey et al., 2017), cardiovascular disease morbidity and mortality (Eriksson et al., 2014; Reynolds et al., 2013) and all-cause mortality (Reynolds et al., 2013).

These findings are compatible with the Developmental Origins of Health and Disease (DOHaD) framework, which suggests that exposure to environmental adversity in the prenatal life may program organs and their functioning in ways that increase risk for physical and mental disorders later in life (Barker, 2004). Programming of the hypothalamic-pituitary-adrenal (HPA) axis has been put forward as one of the mechanisms that may play pathophysiological role (Duthie and Reynolds, 2013; Räikkönen et al., 2010; Seckl and Meaney, 2004).

Yet, to the best of our knowledge only a handful of studies have focused upon the associations between maternal overweight and obesity during pregnancy and offspring HPA axis activity in humans. In one of these studies severe maternal obesity (BMI $\geq$ 40 kg/m^2) measured in early pregnancy was associated with higher salivary cortisol reactivity in response to a delayed gratification test in the 3-5-year-old offspring (Mina et al., 2017). In one other study maternal pre-pregnancy BMI, calculated from retrospectively reported weight after pregnancy and measured height, was not associated with the 4-5-year-old offspring salivary cortisol morning peak or diurnal decline sampled across three points: upon arrival at preschool in the morning, before lunch and in the afternoon upon arrival back to the child's home. This same study also reported that maternal early pregnancy BMI was not associated with salivary cortisol reactivity in response to four challenge tasks (drawing a 'perfect' circle, solving a puzzle, waiting as the examiner wrapped up a favourite prize the child had previously chosen, getting the least favoured prize instead of the most favoured one) (Elhassan et al., 2015). Maternal early pregnancy BMI, derived from medical records, was not associated with cortisol measured from a morning plasma sample in the 8.5-year old offspring (Phillips et al., 2005). A recent study also showed that maternal severe obesity in early pregnancy, derived from medical records, was not associated with cortisol, corticosterone or 11-dehydrocorticosterone measured from fetal cord blood plasma collected at delivery (Stirrat et al., 2017).

Differences in the study set ups in these previous studies (e.g., cortisol measured from saliva, peripheral blood or cord blood plasma; number of samples taken; variation in time point(s) of measurement and types of stressors employed) may possibly explain the mixed findings. Further, the sample sizes have been relatively small and follow ups have been limited to childhood. As the HPA-axis may undergo age-related changes (Gunnar et al., 2014; Lupien et al., 2009), it is important to know if maternal overweight and obesity are associated with offspring HPA-axis activity when measured in adulthood.

Thus, we tested if maternal early pregnancy BMI was associated with diurnal salivary cortisol in a large sample of their offspring followed up from birth to the mean age of 25.3 years. As maternal early pregnancy overweight and obesity have been shown to be associated with higher BMI and fat mass in the offspring throughout childhood to adulthood (Eriksson et al., 2015; Godfrey et al., 2017; Kaseva et al., 2018), as higher BMI in a general population (Adam et al., 2017) and in pregnant women is associated with lower HPA-axis activity (Aubuchon-Endsley et al., 2014; Berglund et al., 2016; Luiza et al., 2015; Stirrat et al., 2016), and as maternal and fetal cortisol levels are correlated (Gitau et al., 2001; Stirrat et al., 2017), we hypothesized that higher maternal early pregnancy BMI would be associated with lower diurnal salivary cortisol of the offspring in adulthood. Further, as also lower levels of BMI have been shown to be associated with lower HPA axis activity in a general population (Kumari et al., 2010), we tested if the associations between maternal early pregnancy BMI and offspring diurnal salivary cortisol were non-linear.

2. Methods

2.1. Participants

Participants come from the Arvo Ylppö Longitudinal Study (AYLS) (Heinonen et al., 2008; Riegel et al., 1995; Wolke et al., 1998) They were recruited from a total of 15,311 deliveries in the seven maternity hospitals in the county of Uusimaa, Finland between March 15, 1985 and March 14, 1986. The sample comprised 2193 infants (1193 boys). Of them 1535 (867 boys; 70% of the total sample of 2193) were admitted to the neonatal wards of the obstetric units, or to the Neonatal Intensive Care Unit (NICU) of the Children's Hospital within ten days after birth. The neonates ranged from severely ill preterm infants to infants requiring only brief inpatient observation. The majority of the admitted infants had no diagnosed illness and were on the ward for observation or because of common problems relating to neonatal adaptation (Heinonen et al., 2008). An additional 658 (326 boys; 30% of the total sample of 2193) infants, not admitted to neonatal wards, were prospectively recruited from births occurring after every second hospitalized infant in the three largest maternity hospitals in the study area during the same period. Details of the study cohort are presented elsewhere (Heinonen et al., 2008; Riegel et al., 1995).

In 2009–2012 the still traceable 1913 (87.2%) participants of the original cohort were invited for a clinical and psychological follow-up (for 107 personal identification number was not available, for 173 participants of the original cohort, addresses were not traceable, they were living abroad or would have needed accommodation for an overnight stay). Of the traceable participants, 1136 participated (59.4%; 51.8% of the original cohort) in the young adulthood follow-up, and of them, 848 participants (74.6%; 38.7% of the original cohort) provided salivary samples for cortisol measurements during one day.

We excluded young adult participants with congenital malformations or chromosomal abnormalities (n = 6), shift workers (n = 3), those who were pregnant (n = 2), and those who did not provide valid salivary cortisol samples (n = 53; 11 had $\geq$2 missing saliva samples out of seven samples, 38 had taken $\geq$2 saliva samples on different days, 3 had one missing sample and $\geq$1 sample(s) taken on different days, and 1 had all seven cortisol values were above the upper limit of assay range (> 100 nmol/L). We additionally excluded participants using inhaled (n = 15) or oral (n = 16) glucocorticoids and nasal corticosteroids (n = 6) because of their effects on cortisol levels. This left us with 747 participants with at least 6 salivary samples; of them data on maternal BMI in early pregnancy were available for 653 participants (327 men; 29.8% of the original cohort). They formed the analytic sample of our study, who at the follow-up were on average 25.3

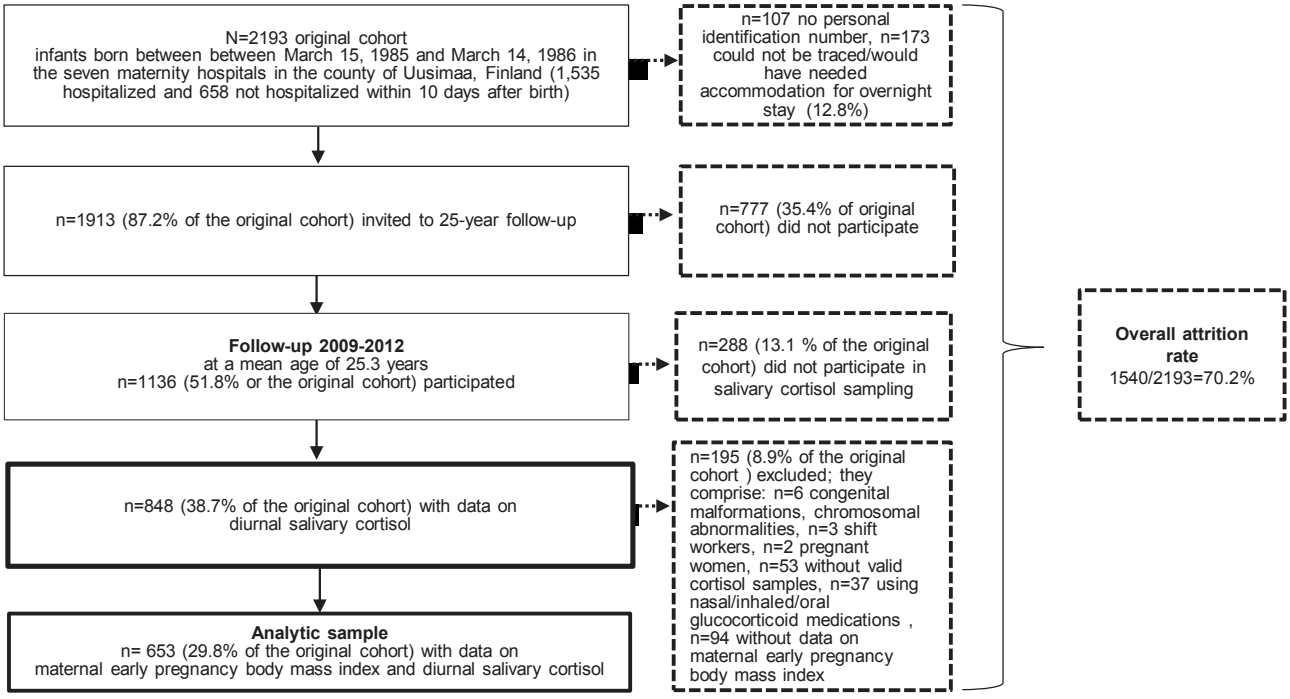

Fig. 1. Flowchart of the participants and sample attrition of the Arvo Ylppö Longitudinal Study.

(*SD* = 0.6, *Range* = 24.4–27.1) years of age. Fig. 1 shows a flow chart of the sample and attrition.

Compared to those participants who were invited but did not participate in the follow-up at a mean age of 25.3-years or who were excluded from the analysis (n = 1260), those who participated in the adulthood follow-up and were included in the analytic sample (n = 653) were less often hospitalized at birth (60.6% vs 72.8%; $p < 0.0001$), were born to older mothers (29.9 vs 29.2 years; $p = 0.001$), had parents with higher education (upper tertiary 34.2% vs 22.1%; $p < 0.0001$), had higher weight (3394 vs 3242 g; $p < 0.0001$) and gestational age at birth (39.1 vs 38.6 weeks; $p < 0.0001$), and were more often women (49.9% vs 43.5%: $p = 0.007$).

The childhood study protocol was approved by ethics committees of the Helsinki City Maternity Hospital, the Helsinki University Central Hospital, and the Jorvi Hospital and in adulthood by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. Informed consent was obtained from the mother when the participants were in childhood. In adulthood written informed consent was obtained from the participating offspring.

2.2. Measures

2.2.1. Maternal early pregnancy BMI

Maternal early pregnancy BMI (kg/m^2), which was calculated from weight and height verified by a nurse at the first visit to the antenatal clinic before 12 weeks of gestation, was extracted from healthcare records. We used BMI as a continuous variable in our analyses. For display purposes we also categorized BMI into pooled underweight (< 18.50 kg/m^2, n = 47) and normal weight (18.5–24.99 kg/m^2, n = 515) and pooled overweight (25–29.99 kg/m^2, n = 76) and obese (≥30 kg/m^2, n = 15) groups, as offspring cortisol concentrations of mothers with early pregnancy underweight and normal weight did not differ (*p-values* > 0.16) and as the number of mothers with obesity was small in our sample.

2.2.2. Offspring diurnal salivary cortisol at a mean age of 25.3 years

Participants collected seven saliva samples during a one-day period: upon awakening (cortisol available for 653 participants; *Mean (M)* = 7:25AM hh:mm, *SD* = 1:17 hh:mm), 15 min (n = 651; *M* = 7:41AM, *SD* = 1:17) and 30 min (n = 650; *M* = 7:57AM, *SD* = 1:17) thereafter, at 10:30AM (n = 645; *M* = 10:35AM, *SD* = 0:29), at noon (n = 649; *M* = 12:13, *SD* = 0:43), at 5:30PM (n = 642; *M* = 5:43PM, *SD* = 0:39) and at bedtime (n = 638; *M* = 11:42PM, *SD* = 1:23). Participants were instructed to avoid brushing their teeth and eating within 30 min after awakening. They were also asked to record the date and time at sample collection. We allowed one missing salivary cortisol sample for analysis; of the participants with at least 6 salivary cortisol samples (n = 653), 66 (10.1%) had at least one missing time value of sampling. Missing sampling times were manually imputed using the pre-determined times of the salivary sampling protocol (e.g., if sampling time of the second salivary sample was missing, but awakening time was recorded, awakening time + 15 min was imputed) or study population mean of the sampling time. Altogether 393 (8.7%) missing salivary sampling times out of 4528 were imputed.

2.2.2.1. Biochemical analyses. Samples were collected between November 2009 and May 2012. Samples were stored at −20 °C and analyzed in May-June 2012 at University of Trier, Germany. Salivary cortisol concentrations were determined by use of a competitive, solid-phase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA; Wallac, Turku, Finland) (Dressendorfer et al., 1992).

Cortisol concentrations were measured in duplicate and averaged. If the second measure was not available, the single concentration measured was used.

The inter-assay coefficients of variation of the control samples were 6.53% for a mean concentration of 3.70 nmol/L, 7.69% for 7.73 nmol/L and 6.88% for 18.38 nmol/L. The intra-assay coefficients of variation ranged between 4.0 and 6.7%.

2.2.2.2. Cortisol parameters. Cortisol values above the upper limit of assay range (> 100 nmol/L) were truncated at 100 (n = 1 at awakening, n = 3 at 15 and 30 min after awakening, n = 2 at 10:30AM, n = 1 at 12:00PM; n = 2 at 5:30PM; and n = 4 at bedtime). As cortisol concentrations in samples from awakening to

bedtime were skewed, we used natural logarithm to normalize their distributions. To study the diurnal average salivary cortisol and the degree of change in salivary cortisol from morning to bedtime (cortisol slopes) we used all seven cortisol values (Hruschka et al., 2005). We also studied average morning (first three samples) and mid-morning to bedtime (samples from 10 A M to bedtime) salivary cortisol averages and slopes. Furthermore, we studied separately salivary cortisol at awakening and at bedtime, and calculated integrated cortisol measures, namely time-weighted area under the curve with respect to ground (AUCg) and time-weighted AUC with respect to increase/change (AUCi) from the three raw morning values (Pruessner et al., 2003) to study the average morning cortisol and cortisol awakening response, respectively. Awakening, bedtime and AUCg and AUCi values were normalized due to skewed distributions using natural logarithm.

2.3. Covariates

We used covariates that either theoretically or according to previous literature are related to maternal overweight/obesity (Gaillard et al., 2011; Torloni et al., 2009; Wang et al., 2013) and/or cortisol secretion (Adam and Kumari, 2009; Kajantie and Räikkönen, 2010; Kudielka and Kirschbaum, 2003; Roche et al., 2013). In Model 1, we adjusted for salivary sampling times for the diurnal cortisol profile analyses, and time of salivary sample at awakening for cortisol awakening, AUCg and AUCi analyses, and at awakening and bedtime for cortisol bedtime analyses, sex hormonal contraception use (women no contraception/women yes contraception/men) and age (years) at salivary collection day.

Model 2 included model 1 covariates plus offspring's BMI (kg/m^2) measured at the follow-up at a mean age of 25.3 years. Model 3 included model 2 covariates plus participant's gestational age at birth (weeks) (Kajantie and Räikkönen, 2010), birth weight standardized for gestational age and sex SD score, maternal age at delivery (years), maternal diabetes (type 1 diabetes, type 2 diabetes or gestational diabetes; yes vs no) and maternal hypertensive disorders (chronic hypertension, gestational hypertension, pre-eclampsia, superimposed pre-eclampsia; yes vs no), smoking during pregnancy (yes/no), parity (primiparous vs multiparous) derived from hospital birth records and highest parental education (primary/lower secondary or less, upper secondary, lower tertiary, upper tertiary) reported by the mother in childhood or reported by the offspring at the follow-up at a mean age of 25.3 years.

Model 4 included model 2 covariates plus offspring's self-reported alcohol consumption (no use or 3–4 times or less often per year, 1–2 times/month, weekly or daily; missing (n = 28) dummy coded as separate category), smoking (yes, ex-smoker, no; missing (n = 9) dummy coded as separate category) and own completed/ongoing education (primary/lower secondary or less, upper/studying for upper secondary, lower tertiary/studying for lower tertiary, upper tertiary/studying for upper tertiary; missing (n = 15) dummy coded as separate category) at the follow-up at a mean age of 25.3 years.

2.4. Statistical analyses

We studied if the offspring daily average and degree of change in the diurnal cortisol from awakening to bedtime (cortisol slopes) varied according to maternal early pregnancy BMI by using random coefficients mixed model regression. In these analyses the seven cortisol values from awakening to bedtime were treated as outcome variables. The models included maternal early pregnancy BMI as a between-person predictor, salivary cortisol sampling time (transformed to SD units, $M = 0$, $SD = 1$; to retain the within-time variation we used the mean of the times across the 7 salivary cortisol samplings) as a time-varying within-person predictor, and their interaction. Covariates were included in the model as fixed effects. We specified an unstructured (UN) covariance matrix and allowed random effects in the model to account for individual differences in the intercept and in the slope.

We re-ran the mixed-model analyses to study if morning (upon awakening and 15 and 30 min thereafter) and mid-morning to bedtime (10:30AM until bedtime) salivary cortisol averages and slopes varied according to maternal early pregnancy BMI.

Further, by using generalized linear models (GLM) with Gaussian reference distribution, we examined if maternal early pregnancy BMI was associated with the offspring salivary cortisol at awakening and at bedtime, and salivary cortisol AUCg and AUCi calculated from the three morning values.

Finally, non-linearity of the associations was tested by adding maternal early pregnancy BMI x maternal early pregnancy BMI interaction into the regression equation in the mixed model regressions and GLMs following the main effect of maternal early pregnancy BMI, and maternal early pregnancy BMI x maternal early pregnancy BMI x cortisol sampling time into the mixed model regressions following their two-way interactions and main effects.

The associations are presented as unstandardized estimates and unstandardized regression coefficients and 95% confidence intervals (95% CIs). The estimates/coefficients reflect change in salivary cortisol in % (units transformed using natural logarithm back-transformed using (exp(estimate/coefficient)-1)*100) per each kg/m^2 unit change in maternal BMI. All associations were adjusted for all covariates in four different models. To control for error rate related to multiple testing, the false-discovery rate (p_{FDR}) was applied setting the false discovery rate across 3 tests (main effects of maternal early pregnancy BMI on diurnal and morning and mid-morning to bedtime salivary cortisol values; maternal early pregnancy BMI x sampling time interactions on diurnal and morning and mid-morning to bedtime salivary cortisol values) for diurnal cortisol mixed model analyses and across 4 tests (salivary cortisol at awakening, at bedtime and AUCg and AUCi) for analyses of cortisol parameters at alpha level 0.05. All analyses were conducted using IBM SPSS 24 (IBM Corp., Armonk, N.Y., USA).

3. Results

Table 1 presents the characteristics of the study sample according to maternal pooled underweight/normal weight and pooled overweight/obesity groups. In comparison to mothers with underweight/normal weight, mothers with overweight/obesity in early pregnancy were older, more often had chronic or gestational hypertension and gestational diabetes and they themselves/their spouses less often had a lower/upper tertiary education. Their offspring were born heavier and had higher BMI at the 25.3-year follow-up.

3.1. Maternal early pregnancy BMI and offspring diurnal, morning and mid-morning to bedtime salivary cortisol averages and slopes

Table 2 shows the findings of the mixed random coefficients regression models. Higher maternal early pregnancy BMI was significantly associated with lower diurnal salivary cortisol average of the offspring (Table 2), but it was not significantly associated with the diurnal cortisol slope from awakening to bedtime (*p-values* > 0.52 in Models1–4 for maternal early pregnancy BMI x salivary cortisol sampling time interaction; data not shown). When we tested the morning and the mid-morning to bedtime averages and slopes, we found that higher maternal early pregnancy BMI was significantly associated with lower morning average cortisol of the offspring (Table 2), but it was not associated with the morning cortisol slope (*p-values* > 0.37 in Models1–4 for maternal early pregnancy BMI x salivary cortisol sampling time interaction; data not shown) or with mid-morning to bedtime cortisol average (Table 2) or slope (*p-values* > 0.44 in Models1–4 for maternal early pregnancy BMI x salivary cortisol sampling time interaction; data not shown). The effect of maternal early pregnancy BMI on diurnal and morning salivary cortisol averages remained significant across adjustments for all covariates (models 1–4 in Table 2). The

Table 1
Characteristics of the sample.

	Maternal early pregnancy body mass index (N = 653)		
	< 25.00 kg/m^2 (N = 562) Mean (SD) /n (%)	≥25.00 kg/m^2 (N = 91) Mean (SD) /n (%)	P for difference
Child characteristics			
At birth			
Sex (boys)	280 (49.8%)	47 (51.6%)	0.75
Gestational age (weeks)	39.1 (2.5)	39.2 (2.4)	0.72
Birth weight (grams)	3359 (697)	3610 (739)	0.002
Birth weight (standard deviation units by sex and gestational age)	−0.1 (1.2)	0.4 (1.2)	< 0.0001
Hospitalized within 10 days of birth			0.97
No	221 (39.3%)	36 (39.6%)	
Yes	341 (60.7%)	55 (60.4%)	
Multiple pregnancy			0.11
Singleton	535 (95.2%)	90 (98.9%)	
Twin	27 (4.8%)	1 (1.1%)	
At 25.3-year follow-up			
Age	25.3 (0.6)	25.3 (0.6)	0.38
Cortisol (nmol/L), geometric means			
At awakening	6.7 (2.1)	5.2 (2.1)	0.003
15 minutes after awakening	8.9 (2.0)	6.89 (2.0)	0.001
30 minutes after awakening	10.49 (1.9)	9.03 (1.8)	0.034
10:30AM	4.39 (2.1)	4.3 (1.9)	0.71
12:00PM	3.46 (2.1)	3.46 (2.0)	1.00
5:30PM	2.05 (2.2)	2.10 (2.5)	0.75
Bedtime	1.01 (2.8)	0.96 (3.4)	0.69
Cortisol parameters (nmol/L)			
Awakening time-weighted area under the curve with respect to ground (AUCg)	339.0 (271.4)	268.6 (215.7)	0.019
Awakening time-weighted area under the curve with respect to increase/decrease (AUCi)	65.5 (160.7)	71.4 (174.6)	0.75
Salivary sample collection time points (hh:mm)			
At awakening	7:27AM (1:16)	7:15AM (1:23)	0.17
15 minutes after awakening	7:42AM (1:16)	7:30AM (1:23)	0.16
30 minutes after awakening	7:58AM (1:16)	7:46AM (1:22)	0.18
10:30AM	10:35AM (0:30)	10:36AM (0:25)	0.85
12:00PM	12:13PM (0:44)	12:13PM (0.37)	0.91
5:30PM	5:42PM (0:39)	5:46PM (0:39)	0.43
Bedtime	11:42PM (1:25)	11:45PM (1:08)	0.72
Hormonal contraception (women)			0.34
No	111 (39.4%)	14 (31.8%)	
Yes	171 (60.6%)	30 (68.2%)	
Body mass index (kg/m^2)	23.6 (4.1)	26.0 (4.7)	< 0.0001
Level of education			0.06
Basic/primary or less	21 (3.8%)	5 (5.6%)	
Upper secondary	166 (30.2%)	33 (37.1%)	
Lower tertiary	138 (25.1%)	28 (31.5%)	
Upper tertiary	224 (40.8%)	23 (25.8%)	
Alcohol consumption			0.91
No	16 (3.0%)	4 (4.4%)	
3-4 times/year or less often	27 (5.1%)	5 (5.5%)	
1-2 times/month or couple of times/month	194 (36.3%)	32 (35.2%)	
Weekly or daily	297 (55.6%)	50 (54.9%)	
Cigarette smoking			0.78
Non-smoker	133 (24.1%)	21 (23.1%)	
Ex-smoker	234 (42.3%)	36 (39.6%)	
Smoker	186 (33.6%)	34 (37.4%)	
Maternal characteristics			
Body mass index (kg/m^2) in early pregnancy	21.2 (1.9)	28.2 (3.4)	< 0.0001
Age at delivery	29.7 (4.8)	31.4 (4.8)	0.001
Parity			0.93
Primiparous	293 (52.1%)	47 (51.6%)	
Multiparous	269 (47.9%)	44 (48.4%)	
Smoking during pregnancy			0.60
No	463 (82.4%)	77 (84.6%)	
Yes	99 (17.6%)	14 (12.4%)	
Diabetic disorders (type 1 and 2 diabetes, gestational diabetes)			< 0.0001
No	530 (94.3%)	78 (85.7%)	
Type 1 diabetes	13 (2.3%)	1 (1.1%)	
Type 2 diabetes	0 (0.0%)	1 (1.1%)	
Gestational diabetes mellitus	19 (3.4%)	11 (12.1%)	
Hypertensive disorders			< 0.0001
Normotensive	471 (83.8%)	60 (65.9%)	
Chronic hypertension	21 (3.7%)	12 (13.2%)	
Gestational hypertension	45 (8.0%)	17 (18.7%)	
Pre-eclampsia, superimposed pre-eclampsia	25 (4.4%)	2 (2.2%)	
Highest education of either parent			0.001
Basic/primary or less	44 (7.8%)	13 (14.3%)	

(*continued on next page*)

Table 1 (*continued*)

	Maternal early pregnancy body mass index (N = 653)	
Upper secondary	103 (18.3%)	30 (33.0%)
Lower tertiary	212 (37.7%	28 (30.8%)
Upper tertiary	203 (36.1%)	20 (22.0%)

Note. Frequencies and percentages refer to valid N of variable. Data are missing as follows: Child characteristics at 25-year follow-up: n = 5 salivary cortisol awakening AUCg and AUCi, n = 1 body mass index, n = 15 educational level, n = 28 alcohol consumption, n = 9 smoking.

associations with diurnal ($p_{FDR} = 0.033$) and morning salivary cortisol averages ($p_{FDR} = 0.017$) remained significant after correction for multiple testing. Fig. 2 illustrates these associations.

We also found significant non-linear U-shaped associations between maternal early pregnancy BMI with diurnal salivary cortisol average ($p = 0.020$-0.026 for maternal early pregnancy BMI x maternal early pregnancy BMI interaction in models 1–4, data not shown) and mid-morning to bedtime salivary cortisol average ($p = 0.042$-0.06 for maternal early pregnancy BMI x maternal early pregnancy BMI interaction). These associations did not, however, survive the correction for multiple testing ($p_{FDR} < 0.017$ for diurnal salivary cortisol average, $p_{FDR} < 0.033$ for mid-morning to bedtime salivary cortisol average).

To exclude any potential bias that may have resulted from imputation of the 393 missing salivary cortisol sampling time points on the findings, we re-ran the analyses by excluding the imputed observations from the analyses; it had no effect on the morning average salivary cortisol ($p = 0.014$); however the association between maternal early pregnancy BMI and diurnal average salivary cortisol was attenuated non-significant ($p = 0.06$). We also re-ran the analyses by excluding the salivary cortisol values that were above the upper limit of assay range (> 100 nmol/L) and which we truncated to 100 nmol/L); it had no effect on the significant findings (*p-values* < 0.031).

3.2. Maternal early pregnancy BMI and offspring salivary cortisol upon awakening, at bedtime and morning AUCg and AUCi

Table 3 shows the findings from the GLMs. Across all adjustment models (models 1–4) and after correction for multiple testing higher maternal early pregnancy BMI was associated with lower salivary cortisol upon awakening ($p_{FDR} = 0.025$) and lower morning salivary cortisol AUCg of the offspring ($p_{FDR} = 0.013$). It was not significantly associated with morning salivary cortisol AUCi or salivary cortisol at bedtime. None of these associations were non-linear (*p-values* > 0.20 for maternal early pregnancy BMI x maternal early pregnancy BMI interaction in models 1–4; data not shown).

4. Discussion

To our knowledge, this is the first study examining associations between maternal BMI measured in early pregnancy before the 12th gestational week and offspring diurnal salivary cortisol in young adulthood. This study showed that higher maternal early pregnancy BMI was linearly associated with lower diurnal salivary cortisol levels. More specifically, per each one kg/m^2 unit increase in maternal early pregnancy BMI offspring average salivary cortisol levels during the day were over -1% lower, and at awakening and on average in the morning they were over -2% lower. While these findings are small in effect size, the differences in the diurnal average, awakening and morning average salivary cortisol levels were over -31% lower between those exposed to the highest and the lowest maternal BMI in our cohort. Maternal early pregnancy BMI was not significantly associated with the degree of change in the diurnal salivary cortisol or morning salivary cortisol, namely diurnal cortisol slope or with cortisol awakening response. It was not either associated with mid-morning to bedtime salivary cortisol average or slope. These associations were independent of the participant's own young adulthood BMI and also remained significant after adjustment for other important covariates related to both the mother and the adult offspring, including maternal diabetic and hypertensive pre-pregnancy and pregnancy disorders, parental education, offspring gestational age, birth weight and attained/ongoing own young adulthood education. The associations were not either explained by nasal/inhaled/oral glucocorticoid medications as their users were excluded from this study sample, and were not accounted for the error rate related to multiple testing. We also tested if any of these associations were non-linear, but none of the non-linear associations survived correction for the error rate related to multiple testing.

The handful of studies that we are aware of that have tested associations between maternal early pregnancy BMI and offspring HPA axis activity have shown that higher maternal early pregnancy BMI is associated with either higher salivary cortisol in the pre-school-aged offspring in response to a delayed-gratification test (Mina et al., 2017), or have shown that it is not associated with the pre-school aged offspring diurnal or stress-induced salivary cortisol, school-aged offspring

Table 2
Associations between maternal early pregnancy body mass index (BMI) and offspring diurnal salivary cortisol at a mean age of 25.3 years.

Maternal early pregnancy BMI (kg/m^2)	Diurnal cortisol from awakening until bedtime (%)			Diurnal cortisol from awakening to 30 minutes after awakening (%)			Diurnal cortisol from 10:30AM until bedtime (%)		
	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P
Model 1	−1.4	(−2.6, −0.2)	0.028	−2.0	(−3.4, −0.5)	0.007	−0.6	(−2.0, 0.7)	0.36
Model 2	−1.3	(−2.6, 0.0)	0.054	−2.3	(−3.8, −0.8)	0.003	−0.5	(−2.0, 0.9)	0.46
Model 3	−1.5	(−2.9, −0.10)	0.036	−2.4	(−4.0, −0.8)	0.004	−1.1	(−2.6, 0.4)	0.15
Model 4	−1.4	(−2.7, −0.1)	0.040	−2.4	(−3.9, −0.9)	0.002	−0.8	(−2.2, 0.7)	0.29

Note. Model 1 refers to adjustment for participant's sex/hormonal contraception, age and salivary cortisol sampling time (all time points between awakening and bedtime for diurnal profile; awakening time, 15 min and 30 min thereafter for analysis from awakening to 30 min after awakening; awakening time and time points from 10:30AM to bedtime for analyses from 10:30AM to bedtime); Model 2 refers to Model 1 covariates plus participant's body mass index in adulthood; Model 3 refers to Model 2 covariates plus participant's gestational age at birth, birth weight SD score standardized by gestational age and sex, maternal age at delivery, parity, maternal smoking during pregnancy, diabetic and hypertensive disorders and parental education at participant's childhood/adulthood; Model 4 refers to Model 2 covariates plus participant's smoking, alcohol consumption and own attained/ongoing education in adulthood.

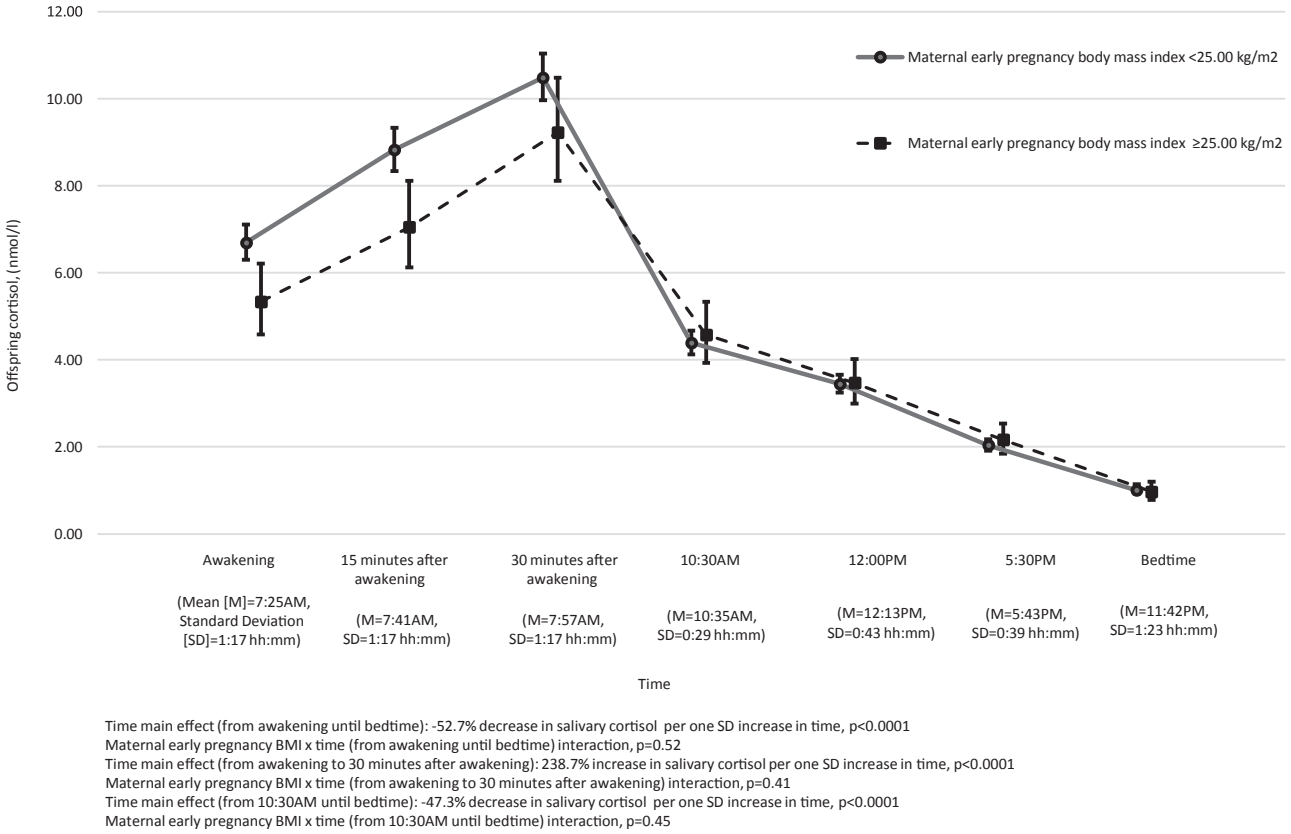

Fig. 2. Associations between maternal body mass index (BMI) in early pregnancy and diurnal salivary cortisol profiles from awakening until bedtime in the offspring at a mean age of 25.3 years. Salivary cortisol geometric means and their 95% confidence intervals are adjusted for time of salivary sampling, offspring sex/hormonal contraception, and age in adulthood.

morning plasma cortisol or cortisol measured from fetal cord blood (Elhassan et al., 2015; Phillips et al., 2005; Stirrat et al., 2017). These studies have, however, examined HPA axis activity in the offspring using study designs that differ from ours (e.g., diurnal cortisol measured upon arrival at day care, before lunch and in the afternoon upon arrival back to the child's home, only once in the morning or in response to stress) and at much younger age than our young adult sample. As our study does not provide data on HPA axis of the offspring in childhood and as the follow-ups of the previous studies do not yet extend to adult age, it remains to be detected if the associations between maternal early pregnancy BMI and offspring HPA axis change according to offspring age. Furthermore, as the HPA axis activity is context-specific, we cannot rule out that contextual factors, such a stress related to the sampling *per se*, may have interfered with our findings. We cannot either account for other environmental factors, such as exposure to stressful life events that may have played a role in re-calibrating the set-point of the HPA axis during the lifespan, as emphasized in the Adaptive Calibration Model (Del Giudice et al., 2011) or in the Lifecycle Model of Stress (Lupien et al., 2009). We were able to account for parental education, offspring own adulthood education and BMI. While lower childhood and adulthood education and higher BMI have been related with physical, social and psychological life adversities and their accumulation over the lifespan (Adler and Newman, 2002; Dixon, 2010; Eurostat, 2010; Mackenbach et al., 2008; Stringhini et al., 2017), they can be considered only as crude proxies. Hence, future studies are needed using longitudinal study design to disentangle the effects on HPA axis activity related to maturation, environmental factors and different study designs.

A recent thorough literature review and meta-analysis on diurnal cortisol slopes demonstrated that flatter diurnal slopes were associated with obesity, depression, internalizing and externalizing problems, fatigue, other mental health problems, inflammation and cancer in general and patient populations (Adam et al., 2017). These are outcomes that have been associated with maternal early pregnancy overweight/obesity (Eriksson et al., 2015; Godfrey et al., 2017; Kaseva et al., 2018; Kong et al., 2018; Rivera et al., 2015) and/or other related prenatal environmental adversities, such as maternal prenatal depression (Kumpulainen et al., 2018; Toffol et al., 2018.). We did not, however, find linear or non-linear associations between maternal early pregnancy BMI and diurnal cortisol slopes, cortisol awakening response or mid-morning to bedtime slopes. Rather, we found linear associations with lower average diurnal and especially lower cortisol levels at awakening and on average in the morning. While the associations of these cortisol measures with the physical and mental health outcomes remain less consistent and less well-established, there is evidence that lower salivary cortisol at awakening (Champaneri et al., 2013; Kumari et al., 2010; Ruttle et al., 2013) and lower average morning cortisol (Champaneri et al., 2013) are correlated with higher BMI and waist circumference, and lower salivary cortisol at awakening and 30 min thereafter are correlated with depression (Sjögren et al., 2006) in general populations.

The biological underpinnings of these associations remain unknown. These include maternal HPA axis activity: maternal overweight, obesity and severe obesity in early pregnancy are associated with blunted maternal HPA axis activity during pregnancy (Berglund et al., 2016; Luiza et al., 2015; Stirrat et al., 2016). Maternal overweight and obesity are also associated with maternal hyperinsulinemia, dyslipidemia, impaired endothelial function, elevated blood pressure and low-grade inflammation during pregnancy (Coussons-Read, 2013; O'Reilly and Reynolds, 2013; Ramsay et al., 2002; Segovia et al., 2014). It is also possible that obesity-related changes in the maternal microbiota (Nehra et al., 2016), and differential exposure to maternal microbiota as a

Table 3
Associations between maternal early pregnancy body mass index (BMI) and offspring diurnal salivary cortisol parameters at a mean age of 25.3 years.

	Cortisol at awakening (n = 653)			Bedtime cortisol (n = 638)			Awakening time-weighted area under the curve (AUCg) (n = 648)			Awakening time-weighted area under the curve with respect to increase/change (AUCi) (n = 648)		
Maternal early pregnancy BMI (kg/m^2)	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P	% per kg/m2 increase in maternal BMI	95% Confidence Interval	P	% per kg/m^2 increase in maternal BMI	95% Confidence Interval	P
Model 1	−2.4	(−4.0, −0.7)	0.007	−1.4	(−3.8,1.0)	0.24	−2.2	(−3.5, −0.8)	0.003	−0.0	(−0.0,0.1)	0.38
Model 2	−2.4	(−4.1, −0.6)	0.009	−1.2	(−3.6,1.3)	0.34	−2.5	(−3.9, −1.0)	0.001	−0.0	(−0.0,0.0)	0.61
Model 3	−2.5	(−4.4, −0.6)	0.010	−2.0	(−4.5,0.7)	0.16	−2.5	(−4.1, −0.9)	0.002	−0.0	(−0.0,0.1)	0.20
Model 4	−2.5	(−4.3, −0.7	0.006	−1.5	(−3.9,1.0)	0.24	−2.6	(−4.0, −1.1)	0.001	−0.0	(-0.0, 0.0)	0.59

Note. Model 1 refers to adjustment for participant's sex/hormonal contraception, age and time upon awakening for analysis of cortisol upon awakening, AUCg and AUCi and to adjustment for participant's sex/hormonal contraception, age and time upon awakening and bedtime for analysis of bedtime cortisol; Model 2 refers to Model 1 covariates plus participant's BMI at adulthood; Model 3 refers to Model 2 covariates plus participant's gestational age at birth, birth weight SD score standardized by gestational age and sex, maternal age at delivery, parity, maternal smoking during pregnancy, diabetic and hypertensive disorders and parental education in participant's childhood/adulthood; Model 4 refers to Model 2 covariates plus participant's smoking, alcohol consumption and attained/ongoing education in adulthood.

result of caesarean section delivery (Papachatzi et al., 2016) and non-breastfeeding (Lepe et al., 2011) which are more common in overweight and obesity, play a role.

Also, epigenetic and genetic factors have been suggested to be play a role. However, a recent epigenome-wide-association-study in over 9000 mother-newborn pairs showed that maternal BMI in early pregnancy had only a small effect on fetal global DNA methylation measured from cord blood (Sharp et al., 2017). Only 8 sites were found to be suggestive of direct causal intrauterine effect by maternal BMI (Sharp et al., 2017). The study suggested that the small effect of maternal BMI at the start of pregnancy on offspring cord blood DNA methylation "may be better explained by genetic or lifestyle factors than a causal intrauterine mechanism" (Sharp et al., 2017). The role of genetic factors remains to be elucidated: a series of genome-wide association studies have unraveled genetic variants related to BMI (Locke et al., 2015) and plasma cortisol (Bolton et al., 2014), but their role in shaping the HPA axis activity in the context of early environment remains largely unknwon. Emerging evidence also suggests that a large proportion of the offsrping DNA methylation is accounted for by the offspring genetic factors and by their interaction with the early enviroment (Teh et al., 2014).

Strengths of our study include a large, longitudinal sample and repeated measurements of salivary cortisol throughout one day from awakening till bedtime. Of the study participants, all had at least six and over 90% (N = 610) had all seven cortisol samples available providing the possibility to reliably study diurnal salivary cortisol profiles. The three salivary cortisol measurements upon and 15 and 30 min after awakening were highly intercorrelated (*intraclass correlations* > 0.76), providing support for the consistency of the morning cortisol assessment. We were also able to account for a wide number of confounders, including the offspring's own young adulthood BMI, and conducted sensitivity analyses to increase internal validity (Adam and Kumari, 2009). We cannot, however, entirely rule out the possibility of residual confounding.

There are limitations to our study. Cortisol sampling was performed on a single day. Cortisol levels may differ substantially within-individuals between sampling days (Clow et al., 2010). However, demanding procedures that include several sampling days may decrease compliance and participation rate (Adam and Kumari, 2009) and in large samples, like ours, increase costs. As participants collected saliva samples in their daily environment, cortisol sampling times were self-reported. While 89.9% of the participants reported all sampling times, 10.1% had a missing recording in at least one of the sampling times (393 of 4528 sampling times were imputed). Some studies suggest that non-compliance may especially influence cortisol awakening response and diurnal slope (Broderick et al., 2004; Kudielka et al., 2003). Yet, the inclusion of time-discordant samples have not been shown to result in differences in cortisol levels or blunted diurnal slopes in a study in which signal-contingent time-sampling protocol was used (Jacobs et al., 2005). In our study, exclusion of salivary cortisol values, for which we imputed the missing sampling time, changed the results only a little. Nevertheless, the inaccuracy related to self-reported sampling times should be borne in mind when interpreting the study findings.

A further study limitation relates to the birth year of our cohort. Over two decades ago when our cohort was born, the prevalence of overweight (11.6% in our cohort) and obesity (2.3% in our cohort) in pregnant Finnish women was much lower than the prevalence in pregnant Finnish women (overweight 20.7%; obese 11.3%) (Kong et al., 2018) and in the world in more recent cohorts (Branum et al., 2016; Deputy et al., 2018; Devlieger et al., 2016; Euro-Peristat, 2013). This clearly limits statistical power and generalizability to cohorts born more recently, but remains an unavoidable limitation when studying today's adult populations. Also lack of data about exposure to ecological stress/positive environment across the offspring lifespan, in addition to lack of data about their somatic health, is a study limitation.

Loss to follow up in longitudinal studies is also inevitable. The follow-up attrition was related to maternal and child perinatal

characteristics. Hence, our findings may not be generalized to populations that vary in characteristics from our study sample.

5. Conclusions

To conclude, our study showed that young adult offspring of mothers with higher BMI in early pregnancy have lower average levels of salivary cortisol during the day, especially in the morning. Whether these findings reflect prenatal programming of the offspring HPA-axis activity warrants further investigation.

Author contributions

Satu Kumpulainen, Katri Räikkönen, and Kati Heinonen had access to all the data and are responsible for the data, for accuracy of the data analysis, and for conducting the research.

Satu Kumpulainen analyzed and interpreted the data, drafted the initial manuscript, and revised the manuscript for important intellectual content. Drs. Eriksson, Heinonen, Kajantie, and Räikkönen contributed to study concept and design, acquisition of data, interpretation of data, and drafting and revising the manuscript for important intellectual content. Dr. Wolke contributed to study design of the childhood assessments, acquisition, processing, and interpretation of data, and drafting and revising the manuscript for important intellectual content. Dr. Lano contributed to assessing the children, acquisition and processing of childhood data and interpretation of the data, and drafting and revising the manuscript for important intellectual content. Drs. Kaseva, Andersson and Reynolds contributed to drafting and revising the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Declarations of interests

Satu M Kumpulainen, Drs. Kati Heinonen, Nina Kaseva, Sture Andersson, Aulikki Lano, Rececca M Reynolds, Dieter Wolke, Eero Kajantie, Johan G Eriksson and Katri Raikkonen declare no conflict of interest.

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