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Ecological salivary cortisol analysis (Part 2): Relative impact of trauma history, posttraumatic stress, comorbidity, chronic stress, and known confounds on hormone levels

Anthony King, PhD, Jennifer Leichtman, BS, James Abelson, MD, PhD, Israel Liberzon, MD, and Julia S. Seng, PhD, CNM
University of Michigan, Ann Arbor, Michigan

Abstract

Background—Although bio-psycho-social health research is an ideal, samples adequate for complex modeling require biomarker specimens from hundreds of participants. Ecological sampling departs from laboratory study norms, with implications for analysis.

Objective—This paper compares salivary cortisol levels and effect sizes of ‘focal’ psychiatric factors, such as trauma history, posttraumatic stress diagnosis, comorbidity, and chronic stress, and ‘nuisance’ factors, including endocrine disorders, medications, physiological factors, such as gestational age, and smoking, to inform ecological study designs.

Study Design—This is a descriptive analysis of ecologically collected cortisol specimens, assayed in an on-going perinatal psychobiological study, addressing methodological considerations.

Results—Focal and nuisance factors are often interdependent with similar effect sizes. Careful specimen deletion decisions and model specification are needed to achieve the hoped-for external validity while maintaining internal validity.

Conclusions—Results of multivariate models support the validity and usefulness of an ecological approach to incorporating biomarkers in health research.

Keywords

ecological validity; salivary cortisol; methodology; posttraumatic stress; community-based research

Introduction

Ecological approaches to health outcomes research call for integrated consideration of biological, psychological, and social factors that all have been shown to affect health (e.g., Krieger, 2001; Rich-Edwards, Krieger, Maisoub et al., 2001; Rowley, 2001). Large-scale epidemiological studies have provided tremendous insight into associations between psychosocial factors and health outcomes, but they cannot separate causal from incidental associations. Laboratory studies can dissect psychobiological mechanisms but cannot directly illuminate the relevance of those mechanisms to public health. A relatively new, translational approach to bridging the gap between the laboratory and “real life” is to include biomarkers taken from laboratory-based, mechanistic studies in large-sample, community-

based research. This approach has much potential for added value, but also has potential pitfalls. In a companion paper (Seng, King, Gabriel et al., YEAR), we presented data suggesting that it is possible to obtain biological specimens from a large, diverse sample and to delete from analysis some of those affected by known sources of ‘nuisance’ error (e.g., medication users, those with endocrine disorders) while maintaining the representativeness of the sample. The question remains whether departures from norms of laboratory science such as applying very few inclusion or exclusion criteria and using unsupervised and mail-in specimen collection procedures could introduce so much error variance as to threaten internal validity. In an effort to bolster the empirical basis for judging the ecological validity of including biomarkers in large-scale studies, we have conducted a series of preliminary, methodological analyses of biomarker data (evening cortisol levels) from a community-based study of perinatal health outcomes in women with stress-related psychiatric disorders. The purpose of this paper is to describe the relative impact on evening cortisol concentration of factors likely to be important in mental and physical health outcomes research, including those that may represent error, confounds, or context, as well as those that are outcomes of primary interest. We consider these factors first in relation to the biomarker, evening cortisol as a dependent variable, and then include cortisol as an independent variable in a multivariate health outcome model for illustrative purposes. To this end, we will present data depicting:

1. Relative effect sizes of individual ‘nuisance’ and ‘focal’ factors,
2. Impact of exclusion decisions on a hypothesis test,
3. Extent of independent associations and inter-correlations,
4. Assessment of an interaction between sociodemographic stress and psychopathology, and
5. Illustration of an ecological model with the biomarker as an independent variable.

1. Background

The hypothalamic-pituitary-adrenal axis (HPA axis) is a major hormonal stress response system that is activated by stressor exposure (reviewed in de Kloet, 2003). While normal HPA axis responses to stressors are adaptive and crucial for survival, excessive or dysregulated HPA axis activity can be maladaptive and have long been postulated to contribute to risk for psychopathology and disease (Holsboer, 2001, Pariante & Miller, 2001). It has been intensively studied as a potential mediator or moderator in the development of stress-related psychiatric disorders such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD; reviewed in Yehuda, 2006) and in the course of stress-sensitive medical illness (e.g., Marin, Martin, Blackwell, Stetler, & Miller, 2007; Rosmond, Holm, & Bjorntorp, 2000). Laboratory studies of patients with MDD have often found hyperactive HPA axis activity, including increased concentrations of cortisol in plasma, urine, saliva and cerebrospinal fluid (CSF) (reviewed in Brown et al., 2004, deKloet, 2003), and relative insensitivity to feedback inhibition (e.g., reduced suppression of cortisol output by dexamethasone). Accumulating evidence also demonstrates HPA axis dysregulation in PTSD, where, in contrast to MDD, laboratory studies have demonstrated reduced circulating cortisol levels and relative hypersensitivity to feedback inhibition (e.g., exaggerated cortisol suppression by dexamethasone; Yehuda, et al., 1993). However, the evidence for altered basal plasma and salivary cortisol levels and 24 hour urinary cortisol secretion in PTSD remains inconsistent and conflicting (Lemieux & Coe, 1995, Mason et al., 1986, Pittman & Orr, 1990, Stein et al., 1997, Yehuda et al., 2002). Contradictory findings may stem from differences between small studies, contradictions that potentially could be resolved if larger samples and models with more variables could increase

ecological validity—enhancing the comprehensiveness of results without unduly sacrificing internal validity.

1.1. Relative effect sizes of individual ‘nuisance’ and ‘focal’ factors

Currently, the majority of studies test hypotheses in models that adjust for a few covariates, but the relative effect sizes of these are not often depicted. Thus the relative impact on cortisol of theoretically important variance or expected error variance variables is not well known. It is possible that some of the variability found in laboratory work could result from the potentially disproportionate impact of uncontrolled contextual or nuisance factors in these small studies. Effect size data are needed for variables that might be variously considered ‘focal’ (e.g., psychopathology), ‘contextual’ (e.g., hardship), or ‘nuisance’ (e.g., having an endocrine disease, smoking) factors, depending on the research question.

1.2. Impact of exclusion decisions on a hypothesis test

In the previous paper we considered the effects on representativeness and cortisol concentration distribution overall when we excluded (by deleting) specimens affected by factors we considered merely sources of error (e.g., endocrine disease). It remains to be seen what consequence such deletions have on hypothesis testing.

1.3. Extent of independent associations and intercorrelations

It is important to consider effects of deletions because even plausibly ‘nuisance’ factors are not always independent of important contextual factors, e.g., they may be confounds. For example, late gestational age entry into prenatal care and thus into a perinatal study is not independent of a contextual independent variable such as sociodemographic stress (Seng, King, Gabriel et al., YEAR). Similarly, the ‘nuisance’ factor of smoking is not independent of our focal psychiatric factor, PTSD diagnosis. Both late entry to prenatal care and smoking are related to adverse health outcomes, making them potential confounds that should be modeled. Thus the extent of interdependence and intercorrelation of multiple factors is important to elucidate. Many factors require such consideration in ecological mental health research, including sex/gender and age, distal personal and environmental factors such as trauma exposure and childhood adversity, and more proximal personal and environmental factors such as comorbidity and adult sociodemographic disadvantage, all of which can affect cortisol profile.

1.4. Assessment of an interaction between sociodemographic stress and psychopathology

In health outcomes research sociodemographic status likely is a proxy for important contextual factors that may interact with focal factors, including psychopathology. Conflicting results of laboratory studies conducted in relation to stress-related psychopathology and cortisol might partly be explained if there have been unrecognized interactions of sociodemographic stress and psychopathology because unintended but *de facto* selection biases have occurred. This could be equally true if other factors, including trauma history are interacting, but unmodelled, factors. The extent to which larger sample ecological studies with more complex analyses can elucidate interactions that should be modeled or strata that should be studied separately.

1.5. Illustration of an ecological model with the biomarker as an independent variable

Finally, it is not yet common to see a biomarker included as an independent variable in a multivariate model, with a health outcome as a dependent variable. Reports of such analysis are needed to determine the extent to which the biomarker is independently associated with a range of outcomes. It is only from accumulated estimating of the relative contribution of

biomarker data over and above the psychosocial factors that we will learn if the extra burden and expense are warranted.

The methodological analysis we present here contributes empirical data to address these questions.

2. Methods

As described in the companion paper in this issue, this is a conceptual, methodological paper using preliminary data from the early months of an ongoing study that uses an ecological approach (R01 NR008767, Psychobiology of PTSD & Adverse Outcomes of Childbearing). That study includes numerous variables that are salient to perinatal and psychiatric research and that are associated with cortisol and health outcomes, making it useful for illustrative purposes. We will conduct this methodological analysis using evening cortisol assay values and psychosocial variables important in ecological frameworks: a proxy for sociodemographic stress, the stress-related risk behavior of smoking, the chronic stressors of lifetime posttraumatic stress disorder and comorbidities, the distal and proximal events of childhood maltreatment and past-year intimate partner violence, and a major life event (pregnancy). The clinical outcomes we will explore will be nausea and vomiting of pregnancy, a condition considered to be stress-related, and potentially associated with psychopathology.

Information about the parent study

Survey and cortisol data analyzed here were collected from June 2005 through October 2006 through an on-going study of the effects of pre-existing PTSD on perinatal outcomes. That study was funded to test the hypotheses (1) that PTSD is associated with adverse perinatal outcomes and (2) that dysregulations in the diurnal pattern of salivary cortisol are associated with both PTSD and adverse perinatal outcomes. We over-sampled African Americans living in poverty, a group at increased risk of adverse perinatal outcomes. Data about trauma exposures, demographics, pregnancy risk behaviors, and psychiatric diagnoses were obtained via standardized telephone interviews. Diurnal salivary cortisol measures were obtained from PTSD-diagnosed, trauma-exposed, but resilient, and non-exposed participants via home-based collection of saliva specimens. Specimens were returned to our laboratory in postage paid mailers provided with the collection kits. The cumulative return rate of saliva specimens analyzed for this paper was 47%. 'Returners' and 'non-returners' did not differ significantly on the 15 demographic, perinatal, and psychiatric characteristics analyzed in the companion paper.

Measures

The variables included in this analysis were measured as follows. Sociodemographic stressors such as poverty, being a pregnant teen, having low educational attainment, and living in the center of Detroit were ascertained via standard items on the CDC's Pregnancy Risk Assessment Monitoring Survey (PRAMS; Gilbert, Johnson, Morrow, Gaffield, & Ahluwalia, 1999), as was information about smoking. Lifetime PTSD was diagnosed via the National Women's Study PTSD Module (Resnick, Kilpatrick, Dansky, Saunders, & Best, 1999; Kilpatrick, Resnick, Freedy et al., 1994). Major depression (MDD) and generalized anxiety disorder (GAD) were diagnosed via the Composite International Diagnostic Interview (Wittchen, 1994). The trauma exposure of childhood abuse was reported via the Life Stressor Checklist (Wolfe & Kimerling, 1997). Recent intimate partner violence was assessed with the Abuse Assessment Screen (McFarlane, Parker, Soeken, & Bullock, 1992). All participants were pregnant and gestational age was estimated by their physician or midwife at a prenatal visit. Saliva specimens analyzed here were obtained prior to eating the

evening meal, ideally in the 4 pm to 6 pm time frame. We are choosing to conduct this preliminary, methodological analysis on the evening specimen because, although laboratory studies have had mixed findings in relation to cortisol and PTSD, more recent studies have found the largest differences using evening cortisol values (e.g., Bremner, Vermetten, & Kelley, 2007; Inslicht et al., 2006; Ranjit, Young, & Kaplan, 2005; Young & Breslau, 2004).

Laboratory processes

Kits arriving by mail were logged into the laboratory tracking system with time lapse between data of the specimen and data of freezing noted. They were frozen at -80 degrees until assay. Each specimen was assayed in triplicate using commercially available Coat-a-Count radioimmunoassay (RIA) kits from Diagnostic Products Corporation (Los Angeles, California). Algorithms are applied to delete values among the triplicates that are outliers. The intra- and inter-assay variability are $<5\%$ and $<10\%$ respectively.

Analysis plan

The series of analyses we conduct are intended to follow the typical process a research team would use to move from data ‘cleaning’ to bivariate and correlational explorations, to multivariate modeling. We proceeded as follows.

2.1. Relative effect sizes of individual ‘nuisance’ and ‘focal’ factors

Ecological sampling will obtain specimens from participants who often would be excluded from laboratory studies in order to reduce error that would undermine internal validity. Because participants affected by defined nuisance factors are excluded, descriptive data and effect sizes of such physiological and pharmacological ‘nuisance’ factors usually are not available to include in research reports. We have an opportunity to quantify the effect on evening cortisol concentration of those with presence or absence of several such sources of error: having an endocrine disorder, taking steroid or antidepressant drugs, steroid hormones that vary by gestational age, and being a smoker. We will be able to compare effect sizes to those for focal and contextual variables: childhood abuse, intimate partner violence, PTSD, MDD, GAD, and sociodemographic disadvantage. We will use independent samples t-tests and estimate effect size using Cohen’s *d*.

2.2. Impact of exclusion decisions on a hypothesis test

We then will assess the impact of deleting participants’ specimens to reduce error by looking at the effects of various deletions on a sample hypothesis. We use a series of t-tests and General Linear Model (GLM) analysis of variance (one-way ANOVA) to determine whether cortisol concentration differs between those with and without lifetime PTSD.

2.3. Extent of independent associations and inter-correlations

The next step is to frame a linear regression model consistent with an ecological approach to examine the independent associations with cortisol concentration of several salient factors simultaneously. We also will present a correlation matrix (using Pearson’s *r*) to provide detailed information about the extent of the inter-correlations.

2.4. Assessment of an interaction between sociodemographic stress and psychopathology

We next will consider one example of a potential interaction by examining sociodemographic stress and PTSD diagnosis together by two different methods. First, we will use a GLM univariate analysis of variance (two-way ANOVA), which also provides effect size (η^2), observed power and adjusted R^2 information. We also will present a stratified analysis, depicting the potential effect of selection bias by studying the association

of PTSD with cortisol concentration in two samples, those with higher versus lower sociodemographic stress.

2.5. Illustration of an ecological model with the biomarker as an independent variable

Since the goal of using biomarkers is to include the biological data as an independent factor in association with a health outcome, our last analysis will be a linear regression model adding the evening cortisol concentration to the independent variables. The illustrative outcome we will use is an indicator nausea and vomiting severity (PUQE score; Koren, Boskovic, Hard, Maltepe, Navioz, & Einarson, 2002) provided as part of the initial pregnancy survey.

3. Results

Because the primary focus of this paper is on cortisol levels we limit attention to the 214 participants who provided an evening cortisol specimen. For reference, we do make some comparisons with the total cohort (n=470). Detailed descriptions of the demographic, perinatal risk and psychiatric status characteristics of the total cohort and of the cortisol returners are included in the companion paper. Briefly, the 214 women whose cortisol levels are analyzed here are 35% African American, 16% teenagers (18–20 years old), 17% living in poverty, 36% with high school education or less, and 35% seeking prenatal care in an urban clinic. Their pregnancies are affected by the following risks: late prenatal care, 36%, past year intimate partner violence, 3.7%, any alcohol consumption in pregnancy, 13%, smoking, 9%, and illicit drug use, 4%. The study oversamples for trauma and PTSD and 22% of returners had childhood abuse, 29% had lifetime PTSD, 7% current PTSD, 12% current major depression, and 7% had current generalized anxiety disorder.

3.1. Relative effect sizes of individual ‘nuisance’ and ‘focal’ factors

Description of the effect sizes of various factors that could affect cortisol—introducing either undesired (error) or desired (focal factor) variance into the data—is shown in Table 1. As expected, physiological ‘nuisance’ factors such as diabetes and gestational age appeared to have medium to large effects on evening cortisol. Being a smoker and smoking within 30 minutes of a sample also had a medium to large effect on cortisol levels. Among the ‘focal’ factors both current PTSD diagnosis and lifetime history of PTSD, but not other psychiatric diagnoses, were significantly associated with elevated cortisol levels in our total cohort. We also found having two or more sociodemographic risk factors was associated with significantly elevated cortisol.

3.2. Impact of exclusion decisions on a hypothesis test

As an illustration of how exclusion of these nuisance factors may reduce error and increase goodness of fit, we examined the apparent effect of lifetime PTSD history on evening cortisol concentration distribution in our sample as subjects having various nuisance variables are excluded in a ‘step-wise’ fashion. Table 2 shows the distribution of focal demographic and psychiatric factors, and a comparison of evening cortisol levels in participants with and without PTSD history in our total cohort of returners (n=214), and in subsequent subsamples as those whose specimens are affected by nuisance factors are excluded (e.g. diabetes or steroid use, undetectable cortisol levels, late gestational age, and smoking). As shown in Table 2, the apparent effect of lifetime PTSD on evening cortisol (i.e. higher cortisol levels in persons with PTSD history compared to no PTSD) becomes stronger when participants with undetectable cortisol levels, endocrine disorders, and late gestation together are excluded; the effect size (η^2), variance explained (R^2), and observed power are all higher in the ‘cleaned’ cohort of n=168, and the significance level improves.

However, when subjects who smoke were excluded, the R^2 , η^2 , and observed power all decrease and the p value becomes non-significant.

3.3. Extent of independent associations and inter-correlations

We next examined the relative independent effects of several factors on evening cortisol in a linear regression model consistent with an ecological approach. We began with the chronic stressor of lifetime PTSD diagnosis and added the stress-related behavioral variables of being a smoker and using alcohol, the intense stressors of childhood abuse and intimate partner violence, and, finally, sum score of sociodemographic disadvantages. We used the 'cleaned' cohort of 168 participants, including the smokers, so that we could control for this potential confound in the regression (shown in Table 3A). The successive models show that the association of PTSD with evening cortisol concentration shares variance with the substance use and sociodemographic factors. When all are taken into account together, being a smoker has the strongest independent association, followed by cumulative sociodemographic stress. The model with all factors included simultaneously is statistically significant ($p < .001$), and the amount of variance explained (adjusted R^2) is 17%. Interrelations among evening cortisol and the independent variables are shown in Table 3B, which shows smoking correlated with PTSD and other abuse history and psychiatric factors, but not related to cumulative sociodemographic stress. Re-running the regression models (data not shown) in the $n=152$ subjects after excluding smokers found a weaker independent association of PTSD with evening cortisol ($\beta = .152$, $p = .084$) after controlling for alcohol, child abuse, and domestic violence, and cumulative sociodemographic risk factors. Cumulative sociodemographic risk factors still had a highly significant independent effect ($\beta = .267$, $p < .001$) after removing smokers, as expected given the lack of demographic differences between smokers and non-smokers reported in the companion paper.

3.4. Assessment of an interaction between sociodemographic stress and psychopathology

To further investigate the potential main effects of cumulative socioeconomic stress on cortisol levels and/or how this contextual factor may influence the effects of focal psychiatric variables on cortisol, we also examined the effects of the accumulation of five specific sociodemographic characteristics we previously identified as potential risk factors for negative mental and physical health outcomes. Our cumulative sociodemographic stress variable is the sum of these dichotomous variables: being African American, pregnant as a teen, living in poverty, having high school education or less, and obtaining prenatal care in the city center. Results of a two-way univariate ANOVA examining the main effects of lifetime PTSD history, cumulative number of sociodemographic stress factors present, and potential interaction effects is shown graphically in Figure 1. The ANOVA found a highly significant ($p < .001$) main effect of presence of two or more sociodemographic stress factors (i.e. increased evening cortisol levels compared to subjects with one or no stress factors), as well as a significant ($p = .024$) main effect of lifetime PTSD on increased cortisol. A nearly significant interaction effect ($p = .066$) of sociodemographic stress by lifetime PTSD was also found. Since we found significant main effects of both PTSD and sociodemographic stress and a nearly significant interaction, we then performed post hoc analyses of effects of PTSD on cortisol level, stratifying the cohort into 'low' and 'high' socioeconomic stress (Table 4). This allows us to observe the effect that potential selection bias could have in laboratory studies if one or the other *de facto* group participated more. The effect size (η^2) and percent of variance explained (adjusted R^2) are largest in the high sociodemographic stress group. The observed power is very low (8%) in the low-stress group, despite their larger sample size ($n=117$), compared with the 41% power in the smaller ($n=51$) high-stress group and the 71% power in the mixed-stress total ($n=168$) cohort.

3.5. Illustration of an ecological model with the biomarker as an independent variable

Table 5 shows results of multivariate linear regression modeling of the 168 women (including smokers), regressing the nausea and vomiting of pregnancy severity (PUQE) score on the ecological factors previously considered. This time we included comorbid disorders, depression and generalized anxiety diagnoses, as well. The biomarker, evening cortisol concentration, is entered last. In these models, both lifetime PTSD and evening cortisol had significant, independent effects (betas $>.180$, $p < .05$) when controlling for these other factors, whereas the other psychiatric diagnoses and ecological factors, including smoking, had no association with this health outcome.

4. Discussion

Using preliminary data from a community-based study of pregnant women selected for trauma exposure and lifetime PTSD diagnosis, this paper presents a ‘test case’ examination of analytical issues that arise when a biomarker is included in a large-scale, ecological health outcome study. In a companion paper (Seng, King, Gabriel et al., YEAR), we showed that it is possible to collect specimens for biomarker analysis (cortisol) from a large, representative sample using telephone and mail procedures, with few protocol deviations or mailing problems. In this paper, we examined the impact of various ‘focal’, ‘contextual’, and ‘nuisance’ factors on cortisol levels, in an effort to model how these various factors might influence detected links between the biomarker, psychosocial predictors, and health outcomes of interest. This approach can broaden and help inform interpretation of data from smaller laboratory studies that use much more highly selected study populations.

4.1. Relative effect sizes of individual ‘nuisance’ and ‘focal’ factors

We found that some ‘nuisance’ biological factors that usually are controlled by exclusion in laboratory studies—endocrine disorders, smoking, and reproductive hormones—had large and medium sized effects on mean cortisol levels in our overall sample. Others, including medication use and protocol deviations had small or negligible effect sizes. Factors we considered ‘focal’ to our illustrative models, including abuse history, sociodemographic stress, and mental health diagnoses had no more than medium effect sizes. This suggests perhaps that exclusion for such ‘nuisance’ factors in laboratory studies is necessary to remove error variance that could obscure relationships of interest. However, if ‘nuisance’ effects are as large as main effects, this raises questions about potential interactions between them that might in fact be of interest, and which could only be studied in larger scale, ecological studies that do not exclude subjects but carefully track all variables with potential impact on outcomes of interest.

4.2. Impact of exclusion decisions on a hypothesis test

Our consideration of which ‘nuisance’ factors to manage by deleting specimens or including them in models illustrates the types of decisions required in the analytic phase of ecological studies. We decided to delete specimens of participants with endocrine disorders because the effect size was large and there were very few in this sample of young pregnant women. Being a smoker also had a large effect size and was relatively rare (10%), but it was not independent of the perinatal and psychiatric characteristics of interest for outcomes research. Therefore, we considered smoking a potential confound and included it in models. It was independently associated with cortisol when the biomarker was the dependent variable, but not with the particular health outcome we modeled as an illustration. Beginning prenatal care in the second half of pregnancy had a medium size effect on cortisol mean level, and it was less rare in our sample (15%). Deleting these participants decreased the proportion of disadvantaged women. For this analysis, we made the decision to delete these 30 specimens nevertheless because (1) we had oversampled disadvantaged women, (2) late gestation was

independent of other perinatal and psychiatric characteristics, and (3) we did not want to use the complex techniques required to model this non-linear relationship.

The complexity of these decisions can be illustrated with a brief consideration of the relations among PTSD, cortisol, and smoking. In these data, as shown in the multivariate model in Tables 4a and 4b, lifetime PTSD history is associated with elevated evening cortisol levels, but this association is potentially influenced by smoking. Smoking has long been known to affect that HPA axis, and is associated with increased salivary and plasma cortisol levels. (Olf et al., 2006) The effect of nicotine on cortisol may be especially pronounced in females, but attenuated in alcoholics (Rasmusson et al., 2006). Our data suggest that failure to control for smoking may lead to serious confounds in any study of salivary cortisol. Smoking has such a large size effect on cortisol levels that inclusion of even a small proportion of smokers may have influential effects on observed levels. However, simple exclusion of smokers could also be problematic – not only does it make samples less representative of the general population, but since several psychiatric disorders are associated with higher levels of smoking, it could bias the subset studied and make it a less representative sample of psychiatric patients. Furthermore, smoking is of high relevance to health research and is generally predictive of adverse health outcomes, and thus investigation of independent and inter-correlated risk and effects from smoking warrants inclusion of smokers in relation to many potential research questions.

This discussion highlights the types of inclusion and exclusion choices that must be made in the analytic phase of ecological studies, if not at the data collection phase. The practice of being transparent about effect size of excluded variables in both laboratory and ecological research reports may be helpful to investigators planning large-sample studies where what is ‘error’ variance and what is ‘data’ is in the eye of the beholder and depends on the research question and the level of statistical complexity planned.

4.3. Extent of independent associations and inter-correlations

Our attempt to model the relationship between lifetime history of PTSD and evening cortisol showed that PTSD was independently associated with cortisol levels, but smoking and sociodemographic stress had even larger effects. The correlation matrix confirmed that all three factors were intercorrelated. Excluding smokers weakened the relationship, showing that this interaction may be of interest or importance, but it would not be discovered in laboratory studies that exclude smokers or never have enough smokers in the small sample to detect their real impact. Excluding smokers does not impact the relationship between sociodemographic stress and cortisol, suggesting that it is an important independent factor to model in ecological health research. These various relationships suggest that the increased sample sizes and multivariate models or stratified analyses possible with an ecological approach may permit resolving of questions that arise when results of small studies conflict.

4.4. Assessment of an interaction between sociodemographic stress and psychopathology

Similarly, our examination of the interaction of sociodemographic and posttraumatic stress in relation to evening cortisol levels indicates that selection bias that can be an artifact of laboratory study designs may be a critical source of error that prevents understanding of stress-related pathophysiology on a public health scale. To the extent that these sociodemographic stress factors (race, poverty, education, adolescence, and center city residence) individually or cumulatively co-vary with psychiatric risk factors and/or with psychiatric diagnoses, they could also represent important moderators (or cofounds) that need to be taken into account and probably measured and controlled for in both laboratory and community-based studies. Consistent with this idea, we found that our cohort of women was really essentially two cohorts with distinct characteristics: a suburban, relatively

affluent, higher-educated, largely European ancestry (White) cohort recruited from perinatal clinics in Ann Arbor, and an urban, relatively poor, lower-educated, largely African ancestry (Black) cohort recruited from perinatal clinics in the center of Detroit.

Our data documented an association of lifetime PTSD diagnosis with altered cortisol levels. However, in contrast to a number of laboratory studies that showed *lower* cortisol levels associated with PTSD, in this community sample we found lifetime PTSD was associated with *higher* levels of evening cortisol. Furthermore, while the ANOVA found a general ‘main effect’ of PTSD, linking its presence to higher cortisol levels, this effect was actually accounted for by an interaction between PTSD with sociodemographic stress, with elevated cortisol seen primarily in those with *both* PTSD and high levels of sociodemographic stress. Presence of sociodemographic stress itself had a highly significant and large ‘main effect’ on cortisol. As seen in Figure 1, PTSD had no impact on cortisol levels within the low sociodemographic stress group, but PTSD was associated with significantly higher cortisol levels within the high-stress group. Had we collected data in only one site, or had we motivated only affluent or poor women to participate, we would not have detected this scientifically interesting and potentially important interaction.

The data from laboratory studies on PTSD and basal plasma, salivary and urinary cortisol levels have in fact been highly inconsistent and conflicting (Lemieux & Coe, 1995, Mason et al., 1986, Pittman & Orr, 1990, Stein et al., 1997, Yehuda et al., 2002). The inconsistencies have been variously attributed to between study differences in sex of samples studied, type of trauma exposure (e.g. combat, Holocaust, sexual assault), presence or absence of early exposure (e.g. childhood adversity / trauma), or presence of psychiatric comorbidities (e.g. MDD or personality disorders; Southwick et al., 2003). Generally, however, ‘contextual’ sociodemographic factors or ‘stressors’ have not been systematically accounted for in the analytical models used in these laboratory studies. Our data demonstrate that sociodemographic factors can have medium size effects on the bivariate relationship between cortisol and PTSD. The impact of sociodemographic stress on cortisol may unknowingly magnify the effects of ‘focal’ factors, for example if there is a concentration of unmeasured disadvantage among subjects with abuse histories and psychopathology. It can also obscure the real impact of a ‘focal’ factor like PTSD, for example if a sample excludes disadvantaged populations.

The data presented here represent the second independent demonstration of an association between lifetime PTSD and *increased* (not decreased) cortisol in a Detroit area community sample (Young & Breslau, 2004), suggesting that it is not an artifact of our somewhat unusual sample (pregnant woman). We used the same commercially available assay kit and found similar mean evening cortisol concentrations and standard deviations, adding support for the empirical findings that cortisol values do not begin to increase until the second half of pregnancy (Challis & Patrick, 1983; Challis, Sprague & Patrick, 1983).

In contrast to these findings from large, diverse samples, we have previously published a small, pilot report suggesting that pregnant women with PTSD in fact had significantly *lower* morning salivary cortisol levels than pregnant women without PTSD (Seng, et al., 2005), consistent with many other small-scale studies. The present results pushed us to re-examine those data, since subjects in that study were recruited from a suburban, academic health center. We found that the cortisol data analyzed in fact came exclusively from affluent non-smokers, a group that the current study suggests will NOT show cortisol elevations linked to PTSD. This closer examination of our own previous data highlights the possibility that a meaningful proportion of the contradictory findings about HPA axis and PTSD may be an artifact of unmeasured or unmodelled sample characteristics, and that ecological models could substantially advance knowledge about general populations, while

still permitting sub-analyses of defined segments of particular interest. Use of biomarkers in ecological studies can reveal scientifically interesting interactions that might otherwise elude detection in laboratory studies, which must exclude rather than analyze potentially confounding contextual factors.

4.5. Illustration of an ecological model with the biomarker as an independent variable

We chose to illustrate use of cortisol concentration as an independent variable in relation to the health outcome of nausea and vomiting of pregnancy because it has been associated with both sociodemographic stress and psychopathology in the literature (reviewed in Seng, Schrot, van de Ven & Liberzon, 2007). Although hormonal factors (e.g., progesterone or human chorionic gonadotropin levels) contribute to nausea and vomiting in pregnancy they do not fully account for who is affected or how severely. This makes this condition a logical exemplar to consider with an ecological biomarker in the model. We found that evening cortisol and lifetime PTSD diagnosis both were independently associated with severity of nausea and vomiting. The biomarker did explain variance independently of the psychosocial factors that could influence cortisol concentrations: trauma history, sociodemographic stress, and psychiatric diagnoses, and smoking. This is a *post hoc* analysis done for purposes of illustration only, but the regression results suggest that if other logically selected biomarkers were added (e.g., salivary progesterone) in a longitudinal design that could incorporate effects of gestational age, we could conceivably determine the extent to which nausea and vomiting of pregnancy is due to stress, psychiatric morbidity, hormone levels or sensitivities, or complex interactions between such factors or within sub-groups. This integrated modeling of biomarkers, psychosocial, and clinical symptom data could rapidly advance knowledge where none of these three types of studies conducted by disparately trained laboratory, social science, or clinical researchers can contribute nearly as much.

Strengths of this methodological paper include the medium sized sample which includes the full range of sociodemographic diversity, from those likely to be minimally to maximally stressed by the context of their lives. Limitations include that all participants are pregnant women, that only half returned cortisol specimens, and that other potentially relevant factors (e.g., body mass index, actual sleep/wake cycle) were not measured. Generalizability of our conclusions may be limited to perinatal studies of early gestation, but the issues relevant to consider in other topics likely are much the same. The extent to which pregnant women may be more or less stressed than the general population cannot be addressed with these data, but the association of PTSD with increased cortisol in the context of sociodemographic stress warrants replication and application to perinatal outcomes research. The presence of this strong interaction within our relatively modest sample size, and the association of cortisol level with the sample outcome of nausea and vomiting, suggests that trauma-informed perinatal research that includes HPA axis biomarkers may, indeed, enhance ability to identify gravidas at increased risk for some complications or adverse outcomes. Although the return rate in our study is lower than other community-based studies, those who returned specimens did not differ from those who did not. The low return rate may be an artifact of pregnancy, such as increased fatigue or nausea, making specimen collection or mailing less likely. This type of low-return could occur in other ecological health studies if participants' health status is lower than population norms. Efforts to improve low return rates by qualitative study of non-returners should perhaps be built into pilot or start-up phases of future studies. Our lack of data about body mass index (BMI; Therrien et al., 2007) or sleep/wake cycle is a limitation that could have been addressed at the planning phase. In mental health research, especially research on PTSD and HPA axis, it is not reasonable to assume that abnormal BMI and abnormal sleep are randomly distributed. With minimal additional response burden these factors could be measured and modeled. Sample sizes in ecological studies should be able to support the addition of two more covariates. Finally, other research

questions important to the field of PTSD, including effect of comorbidity of PTSD with MDD, were not addressed in this methods paper, but have been shown to be important in other ecological studies (Young & Breslau, 2004).

In conclusion, placing the results of these methodological analyses into the context of previous research, we find support for the ecological validity of the cortisol values obtained. The descriptive data presented here and the results of the sample models illustrate the potential value of an ecological approach that incorporates biomarkers into studies where large samples are well-characterized on several levels of environmental and personal variables. It appears feasible to quantify error from nuisance factors, including deviations from data collection protocols. As more investigators adopt an ecological approach, more sophisticated analytic tools to cope with specific aspects of such variance may become available (e.g., Ranjit et al, 2005). The large sample sizes should permit the type of multivariate modeling and sub-group analyses that may result in faster, more reliable translation from laboratory bench to health care encounter and on to the health and social policy arenas.

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Figure 1.

Effects of level of socioeconomic risk factors (low risk having < 2, high risk having >2 factors) and lifetime PTSD diagnosis on evening salivary cortisol levels. Bars show mean cortisol level by cell, error bars show SEM. Factorial ANOVA found main effects on evening cortisol levels of both socioeconomic risk ($F[1, 164] = 13.98, p < .001$, observed power .961) and lifetime PTSD diagnosis history ($F[1, 164] = 5.19, p = .024$, observed power .619), and a nearly significant interaction effect (risk $\times$ PTSD history interaction effect $F[1, 164] = 3.42, p = .066$, observed power .451). Adjusted model $R^2 = .102$

Table 1

Description and effect size for differences in evening cortisol concentration by presence versus absence of 'nuisance,' 'focal,' and socioeconomic stress characteristics.^a

Factors	Rate in Sample	Present mean (SD)	Absent mean (SD)	<i>t</i>	<i>p</i>	<i>d</i>	Effect size
Nuisance factors thought to affect cortisol levels							
Endocrine disease, diabetes ^b	0.5 (1)	.3100 (na)	.1442 (.14)	-1.2	.243	1.675	large
Corticosteroid oral, inhaler	2.5 (5)	.1720 (.13)	.1435 (.14)	-.4	.656	.211	small
Psych medication, SSRI	0.5 (1)	.1103 (na)	.1437 (.14)	.2	.815	-.247	small
Gestational age >20 weeks ^c	15.2 (30)	.2434 (.23)	.1259 (.11)	2.7	.010	.651	medium
Being a smoker	9.5 (16)	.2346 (.20)	.1144 (.09)	-2.4	.032	.775	large
Smoking <30 minutes prior	1.8 (3)	.3280 (.44)	.1222 (.10)	-.8	.502	.645	medium
Eating <30 minutes prior	17.9 (30)	.1397 (.15)	.1229 (.10)	-.7	.458	.132	
Being >1 hour early/late	18.5 (31)	.1037 (.06)	.1309 (.12)	1.2	.222	-.287	small
Focal factors in mental health studies							
Childhood abuse history	23.2 (39)	.1297 (.14)	.1247 (.10)	-.2	.808	.041	
Past year domestic violence	3.6 (5)	.0951 (.06)	.1270 (.10)	.7	.495	-.387	small
Lifetime PTSD	32.1 (54)	.1570 (.16)	.1111 (.07)	-2.0	.048	.371	small
Current PTSD	6.5 (11)	.1935 (.14)	.1211 (.11)	-2.1	.038	.575	medium
Current MDD	11.3 (19)	.1682 (.18)	.1205 (.10)	-1.1	.278	.327	small
Being in SES group with >2 risks	30 (51)	.1742 (.16)	.1048 (.08)	-3.0	.004	.559	medium

^a 9 women who returned other specimens did not return the evening tube, and 9 specimens with values = .00 removed prior to all analyses for this table.

^b 7 specimens from women with diabetes, steroid medication, or psychotropic medications were removed for subsequent analyses.

^c 30 specimens from women completing the interview >20 weeks gestation removed for subsequent analyses. na=not applicable because n=1.

Table 2

Effects of Specimen Exclusions to Reduce Error on a Sample Hypothesis Test of PTSD Association with Evening Cortisol Concentration using Univariate ANOVA

Subgroups	Lifetime PTSD				No PTSD				Univariate ANOVA					
	total n	mean		SD	n	mean		SD	n	F	p	eta2	Obs power	adj R2
		cortisol				cortisol								
All returners	214	0.1701	(.20)	61	0.1265	(.20)	153	4.215	0.041	0.019	0.533	0.015		
Undetectable levels excluded	205	0.1729	(.20)	60	0.1326	(.10)	145	3.35	0.069	0.016	0.445	0.011		
Endocrine dx and med users excluded	198	0.1729	(.20)	60	0.1309	(.20)	138	3.702	0.056	0.019	0.482	0.014		
Late gestation out	168	0.1570	(.16)	54	0.1109	(.16)	114	6.37	0.013	0.037	0.709	0.031		
Smokers excluded	152	0.1302	(.12)	44	0.1010	(.07)	108	1.890	0.171	0.012	0.277	0.006		

Table 3

3a

Multivariate Hierarchical Linear Regression of Evening Cortisol as the Dependent Variable

Factor	β	t	Sig
1. Lifetime PTSD	.192	2.524	.013
2. Lifetime PTSD	.133	1.782	.077
Any alcohol during pregnancy	-.081	-1.082	.281
Being a smoker during pregnancy	.307	4.000	.000
3. Lifetime PTSD	.189	2.209	.029
Any alcohol during pregnancy	-.080	-1.071	.286
Being a smoker during pregnancy	.308	4.016	.000
History of child abuse	-.056	-.676	.500
Domestic violence in last year	-.106	-1.386	.168
4. Lifetime PTSD	.176	2.101	.037
Any alcohol during pregnancy	-.081	-1.107	.270
Being a smoker during pregnancy	.302	4.033	.000
History of child abuse	-.077	-.942	.347
Domestic violence in last year	-.141	-1.869	.063
Number of SES risk factors	.218	2.962	.004

3b

Inter-correlations between Factors

Factors	Cortisol	PTSD	EtOH	Smoke	Socio Risk	Child abuse
Evening Cortisol	1.000	0.192*	0.000	0.316**	0.258**	0.049
Lifetime PTSD		1.000	0.073	0.211**	0.173*	0.472**
Alcohol during pregnancy			1.000	0.235**	0.007	0.056
Smoking during pregnancy				1.000	0.061	0.144*
Sociodemographic risk					1.000	0.163*
Child abuse history						1.000

Note. Model 1, $F[1,166] = 6.37$, $p = .013$, adjusted $R^2 = .031$. Model 2, $F[3,164] = 7.64$, $p < .001$, adjusted $R^2 = .107$; change in R^2 $p < .001$. Model 3, $F[5,162] = 5.13$, $p < .001$, adjusted $R^2 = .110$; no significant change in R^2 ; Model 4, $F[6,161] = 5.94$, $p < .001$, adjusted $R^2 = .151$; change in R^2 $p < .004$.

Effect of Selection by High or Low Sociodemographic Stress (low, 0 or 1 stressors versus high, > 2 stressors) on Sample Hypothesis Test of PTSD Effect on Evening Cortisol Levels

Table 4

Sociodemographic Group	Lifetime PTSD			No PTSD			F	p	eta2	Obs power	Adjusted R2
	Mean		SD	Mean		SD					
	Cortisol	n		Cortisol	n						
Total cohort (n=168)	0.1570	54	(.16)	0.1110	114	(.07)	6.371	0.013	0.037	0.709	0.031
High stress (n=51)	0.2149	24	(.19)	0.1381	27	(.10)	3.117	0.084	0.063	0.411	0.044
Low stress (n=117)	0.1107	30	(.10)	0.1027	87	(.06)	0.247	0.620	0.002	0.078	-0.007

Table 5

Hierarchical regression of Gestational Vomiting (PUQE Score) by Psychosocial and Biological Factors

Factor	β	t	Sig.
1. Child abuse/neglect	-.026	-.340	.735
2. Child abuse/neglect	-.020	-.260	.795
Sociodemographic stress factors	-.047	-.599	.550
3. Child abuse/neglect	-.080	-.972	.333
Sociodemographic stress factors	-.077	-.961	.338
Lifetime PTSD diagnosis	.214	2.321	.022
MDD current	-.057	-.665	.507
GAD current	-.005	-.057	.954
4. Child abuse/neglect	-.080	-.966	.336
Sociodemographic stress factors	-.077	-.948	.344
Lifetime PTSD diagnosis	.214	2.311	.022
MDD current	-.056	-.636	.526
GAD current	-.005	-.058	.954
Smoker	-.006	-.069	.945
5. Child abuse/neglect	-.066	-.801	.424
Sociodemographic stress factors	-.119	-1.447	.150
Lifetime PTSD diagnosis	.193	2.087	.038
MDD current	-.056	-.651	.516
GAD current	-.001	-.013	.989
Smoker	-.055	-.655	.513
Evening Cortisol	.183	2.174	.031