HHS Public Access

Author manuscript

Psychoneuroendocrinology. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Psychoneuroendocrinology. 2021 January ; 123: 105041. doi:10.1016/j.psyneuen.2020.105041.

The Association of Cortisol Curve Features with Incident Diabetes among Whites and African Americans: The CARDIA Study

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Abstract

Introduction: A flatter diurnal cortisol curve has been associated with incident diabetes among older white adults. However, this relationship has not been examined among middle-aged individuals or African Americans [AA]. We analyzed the longitudinal association of baseline diurnal cortisol curve features with incident diabetes over a 10 year period in a cohort of AA and white participants who were, on average, 40 years old.

Methods: Salivary cortisol was collected immediately post-awakening, then subsequently 45 minutes, 2.5 hours, 8 hours, and 12 hours later, as well as at bedtime. Cortisol curve features

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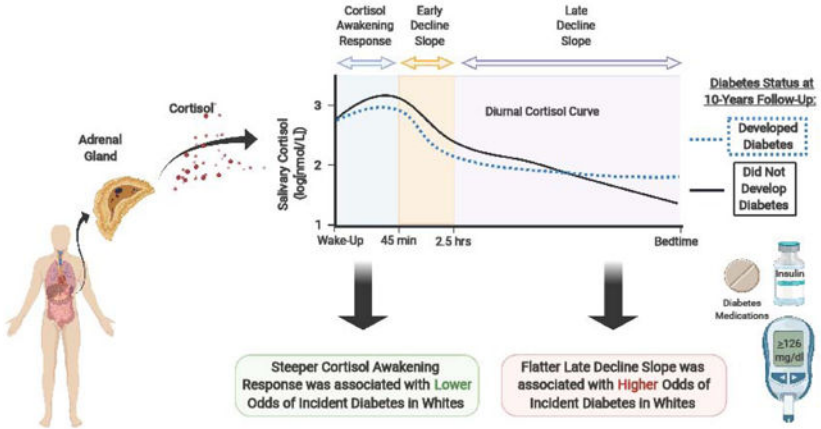
The authors have no conflicts of interest to declare.

included wake-up cortisol; cortisol awakening response (CAR); early, late, and overall decline slopes; bedtime cortisol; and 16-hour area under the curve (AUC). Salivary cortisol (nmol/L) was log-transformed due to positively skewed distributions. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL or taking diabetes medication. Logistic regression models were used to investigate the association of log-transformed cortisol curve features with incident diabetes. The analysis was stratified by race and adjusted for age, sex, education, depressive symptoms, smoking status, beta-blocker and steroid medication use and BMI.

Results: Among 376 AA and 333 white participants (mean age 40 years), 67 incident diabetes cases occurred over 10 years. After full adjustment for additional covariates, a 1-unit log increase in CAR was associated with a 53% lower odds of incident diabetes among whites (Odds Ratio [OR] 0.47, 95% CI: 0.24, 0.90). A 1-SD increase in late decline slope was associated with a 416% higher odds of incident diabetes among whites (OR 5.16, 95% CI: 1.32, 20.20). There were no significant associations in AAs.

Conclusion: A robust CAR and flatter late decline slope are associated with lower and higher odds of incident diabetes, respectively, among younger to middle-aged whites and may provide a future target for diabetes prevention in this population.

Graphical Abstract



Keywords

Cortisol; Diabetes; African American; hypothalamic-pituitary-adrenal axis

1. Introduction:

Hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, characterized by a flattened diurnal cortisol profile, is cross-sectionally associated with type 2 diabetes (T2D) and with several conditions that promote T2D, including obesity and insulin resistance [1–3]. Cortisol promotes hyperglycemia indirectly through free fatty acids and central adiposity [4]. Cortisol induces a catabolic state by upregulating lipolysis and proteolysis. As a consequence, free fatty acids increase with metabolites (ceramides, diacylglycerols, and long-chain acyl-CoA), promoting hyperglycemia through the disruption of insulin signaling

[5]. Glucocorticoids also promote redistribution of adipose tissue from peripheral to central depots with an abundance of glucocorticoid receptors in the visceral adipose tissue of central depots compared to subcutaneous adipose tissue [4]. In addition to its indirect effects on glycemia, cortisol directly: 1) promotes hyperglycemia through induction of hepatic genes responsible for gluconeogenesis [6]; 2) increases skeletal muscle insulin resistance through inhibition of glucose transporter GLUT 4 translocation to the cell surface [6]; and 3) modulates insulin secretion [6]. Cortisol concentrations throughout the day follow a classic circadian pattern. Levels are relatively high at wake-up. In the 30–45 minute period following wake-up, cortisol levels increase dramatically and reach their daily peak (cortisol awakening response [CAR]). Thereafter, levels fall throughout the day (early decline and late decline) and reach their daytime nadir at bedtime [7].

A less dynamic diurnal cortisol curve, characterized by a blunted CAR, flatter decline slopes, and/or higher bedtime cortisol level, has been linked with mental and physical health outcomes [7,8] and has been proposed as an indicator of HPA-axis dysfunction [7–9]. The physical health outcomes include incident diabetes and worse glycemic control among those with diabetes [7–11]. Diurnal cortisol curve profiles are influenced by factors such as age [12,13], sleep duration and quality [14] and psychosocial stress [15,16]. Whether changes in the specific features of the cortisol curve are directly impacting deleterious health outcomes through glucocorticoid receptors or inflammation or are markers of upstream biological factors is an area of investigation [8,17]. Some components of the diurnal cortisol curve, including AUC and the diurnal cortisol decline slope, are hypothesized to represent increased overall cortisol exposure [18,19]. In contrast, other features including the CAR may be more representative of the reactivity or function of the HPA axis [20–22]. Thus, chronobiology, including the level and timing of cortisol exposure, may be critical in understanding the role of cortisol in glucose metabolism.

Although a flattened diurnal curve and higher bedtime cortisol have been associated with dysglycemia and incident diabetes in non-Hispanic whites (whites) [10,23], no study has yet to fully elucidate possible racial differences among whites and AAs in the longitudinal relationship between diurnal cortisol curve features and incident diabetes. Notably, there are significant differences in the diurnal cortisol pattern between African Americans (AAs) and whites. AAs have higher evening salivary cortisol and an overall flatter diurnal curve, independent of socioeconomic status [24,25]. From an environmental perspective, differences in the diurnal cortisol pattern between AAs and whites may be partially explained by shorter sleep duration in AAs [14,26]. The prevalence of short sleep (< 6 hours) among African Americans is greater than 40% and AAs have worse sleep quality compared to whites [27]. Another potential factor is discrimination, a social stressor, wherein repeated exposure to it over time leads to flatter diurnal cortisol slopes among racial/ethnic minorities [16] and in general populations [15]. In the United States, AAs experience discrimination at higher rates than other racial/ethnic groups including whites [28]. Thus, shorter sleep duration and discrimination may be two significant causes of differences in diurnal cortisol patterns in AAs. From a genetic perspective, evidence suggests that heritability of cortisol levels at wake-up and 30 minutes post wake-up is high, whereas evening cortisol levels lack heritability among adults [29]. However, to our

knowledge, no study has assessed the role of genetics or epigenetics in diurnal cortisol pattern differences between AAs and whites.

In this study, we aimed to analyze the association of baseline diurnal cortisol curve measures with incident diabetes over 10 years among middle-aged white and AA participants. The primary aims of the study were to examine the association between features of the diurnal cortisol curve with incident diabetes and to assess potential differences in outcomes between white and AA participants by conducting a stratified analysis. We hypothesized that a lower wake-up cortisol, attenuated cortisol awakening response (CAR), flatter decline slopes and higher bedtime cortisol would be associated with incident T2D over a ten-year period among both white and AA participants.

2. Methods:

2.1. Study Population:

The Coronary Artery Risk Development in Young Adults (CARDIA) Study was a longitudinal observational cohort study initiated between 1985 and 1986. CARDIA was designed to investigate the development of cardiovascular disease (CVD) and risk factors associated with its progression among AA and white adults aged 18–30 years of age from Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California [25]. Further details regarding the study design have previously been described [30]. Between 2000 and 2001, participants from the Chicago and Oakland sites living within a 50-mile radius of the participating clinics were recruited into a sub-study examining socioeconomic status and biological risk in the development of CVD, which included the assessment of salivary cortisol. Eight-hundred and ten adults aged 32–51 years were included in this CARDIA ancillary study and underwent baseline examinations between 2000–2001 (Year 15) with subsequent follow-up assessments in 2005–06 (Year 20) and 2010–11 (Year 25). The CARDIA study was approved by institutional review committees at each respective location and all participants gave informed consent.

2.2. Cortisol Measures and the Assessment of Cortisol Curve Features:

The output of cortisol follows a distinct circadian rhythm reaching a peak 30–45 minutes after waking, declining steadily throughout the day and reaching a nadir close to midnight [7]. In the CARDIA study, six salivary cortisol samples were obtained on a single weekday as part of the ancillary study at the Year 15 exam. These samples were collected immediately post-awakening, then 45 minutes, 2.5 hours, 8 hours and 12 hours later and at bedtime. Participants were provided with alarm watches calibrated to their wakeup times and time intervals described above to serve as directives to collect saliva using cotton swabs throughout the day. During sampling, participants were directed to keep the cotton in their mouths for 30 seconds. Once fully saturated with saliva, the samples were placed in salivettes, which were stored at room temperature at participants' homes and brought to their respective clinics the following day. Samples were then kept frozen until assessed via time-resolved immunoassay with fluorometric end point detection [25,31]. Intra-assay variation was less than 12% and samples containing sub-detectable levels of cortisol were assigned a value of 0.5 nmol/L [25]. The six collections were used to define cortisol curve parameters

including wake-up cortisol, the cortisol awakening response (CAR; 0 to 45-min post-awakening rise), early decline slope (45-min to 2.5-hour post awakening decline), late decline slope (2.5 hour to bedtime decline), overall decline slope (wakeup to bedtime; excluding 45-min post awakening), and bedtime cortisol [11,25]. The total area under the curve (AUC), a time-adjusted measure of total cortisol exposure while awake, was defined by the plot of log-transformed cortisol values against the collection times divided by the duration, in hours, between the first and last sample. The AUC measure was computed only for those who had data for at least 4 samples and a minimum of 12 hours between the first and last sample. In this paper, we call this standard AUC the 16-hour AUC because we restricted our samples only up to 16 hours after wakeup.

2.3. Outcomes Assessment:

Fasting plasma glucose (FPG) and insulin were measured with blood drawn by venipuncture and processed at the central laboratory according to a standard protocol. Glucose was assayed using the hexokinase coupled to glucose-6-phosphate dehydrogenase method by Linco Research (St. Louis, MO, USA). Individuals were considered to have impaired fasting glucose (IFG) if FPG was between 100–125 mg/dL. T2D was defined as FPG ≥126 mg/dL or taking diabetes medication. T2D status was assessed at years 20 and 25. Individuals that developed T2D at year 20 were censored and were considered incident at year 25. The radioimmunoassay for insulin required an overnight, equilibrium incubation and used a unique antibody that has less than 0.2% cross-reactivity to human proinsulin and its primary circulating split form Des 31, 32 proinsulin (Linco Research, St. Louis, MO, USA).

2.4. Covariates:

Demographic and socioeconomic factors previously shown to be associated with features of the cortisol curve were collected at Year 15 and subsequently used as covariates in the models [7,25,32]. Information regarding age, sex, education (years of schooling), cigarette smoking (current smoking versus not), current medications (including beta blockers or steroids) and Center for Epidemiologic studies depression scale (CES-D), were obtained during clinical interviews or questionnaires in accordance with the study design [25,30]. Information regarding the development, reliability, and generalizability of the CES-D scale has been described [33]. The overall diurnal profile tends to become flatter with age [12,13]. Men have higher maximum, trough, and total AUC cortisol than women [13,24]. Higher levels of education among whites and blacks is associated with higher wake-up cortisol [34]. Specifically, among whites it is associated with a more robust CAR and among AAs is associated with higher cortisol throughout the day [35]. Current cigarette smoking status is associated with higher total AUC cortisol and an overall flatter diurnal cortisol decline [13,36]. In the Study of Women's Health Across the Nation (SWAN), higher CES-D scores were associated with flatter diurnal cortisol slopes [37]. In addition to being associated with the diurnal cortisol profile, lower levels of educational attainment, active cigarette smoking and depression are associated with an increased risk of T2D [38–40]. Consistent with a similar analysis, we used categorical BMI to adjust for adiposity [10]. Adiposity measures included both BMI and waist circumference. The former was calculated by weight (in kilograms)/ height^2 (in meters), while the latter was assessed through measurement of the circumference around the umbilicus.

2.5. Statistical Analysis:

Our analysis was restricted to participants with complete diurnal cortisol curve features (exposure) and data on outcomes and important covariates. Following exclusion of those with diabetes at baseline (n=29), missing data on exposures (n=57) and important covariates (smoking status [n=1], BMI [n=3] and CES-D score [n=11]), the final primary analytical cohort consisted of 709 participants (Figure 1, Exclusion Cascade). Differences were observed in the diurnal cortisol curve between individuals that woke up prior to and after 11 A.M. Thus, those that woke up after 11 A.M. (n=18) were excluded in a secondary analytical cohort consisting of 691 participants [25].

Baseline characteristics of participants at Year 15 were presented and stratified by race and the development of diabetes during follow-up using chi-square for categorical variables and two-sample t-test for continuous variables. As a result of positively skewed distributions, all cortisol curve values were log-transformed. We used logistic regression models to calculate the odds ratios (OR, 95% confidence interval [CI]) of incident T2D by log-transformed salivary cortisol curve measures among all participants with a race-interaction term in the model to give race specific estimates of the effect of cortisol measures. For the non-slope cortisol curve features, to calculate the OR for a 1-unit increase in log cortisol curve features, we fit a logistic regression model with log cortisol curve features as the predictor. The regression coefficient reflects the change in log-odds for a 1-unit change in log cortisol curve features. Through exponentiation of the regression coefficient, the OR per 1-unit change in log cortisol curve features can be estimated. To calculate the OR for a one standard deviation (SD) change in the early, late and overall decline slopes, we fit a logistic regression with a standardized predictor. Standardizing centers and scales the predictor such that it has a mean of zero and a SD of one. Thus, a 1-unit change in the standardized predictor coincides with a 1-SD change on the original scale. The OR per 1-SD change in the early, late and overall decline slopes was estimated via exponentiation of the regression coefficient. P-values for interaction effects were not adjusted for multiple comparisons and are reported here as preliminary data for descriptive purposes. We tested for effect modification by race using the following equation for the unadjusted models: $\text{logit}(P(\text{diabetes} = \text{Yes})) = \beta_0 + \beta_1 \times (\text{Cortisol Curve Feature}) + \beta_2 \times (\text{Race}) + \beta_3 \times (\text{Cortisol Curve Feature} \times \text{Race})$. We used the likelihood ratio test to assess the statistical significance of the coefficient (β_3) on the interaction term. In this equation, β_3 is interpreted as the difference between the log-odds ratio corresponding to a change in wake-up cortisol by 1-unit among AAs and the log-odds ratio corresponding to an increase in wake-up cortisol by 1-unit among whites. Statistical significance was defined as two-sided alpha <0.05 in the main analysis. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results:

The 709 participants were majority female (58%) and non-smokers (82%). The average educational attainment was greater than high school (14.96 ± 2.47 years of education) and BMI was 29.25 ± 7.24 kg/m^2 (Table 1). The cohort had a relatively even distribution of white and AA participants. White participants were 40.4 years of age compared to 39.6

among AAs with more years of education, and lower current smoking, CES-D scores, BMI, waist circumference and fasting insulin compared to AAs (Table 1). Whites had higher wake-up cortisol, steeper late decline slope, and a lower bedtime cortisol than AAs ($p<0.01$). Among all participants, those who developed T2D over the 10-year period had significantly higher bedtime cortisol levels ($p<0.01$) and showed a trend towards having a blunted CAR ($p=0.05$), as well as flatter late decline slopes ($p=0.08$) compared to those that did not develop T2D (Supplementary Table 1). Baseline characteristics of the 691 participants included in the secondary analysis are presented in Supplementary Table 2. Individuals that were excluded on the basis of waking up after 11 A.M were less educated with higher BMI and waist circumference (all $p<0.05$). Furthermore, excluded participants had lower wake-up cortisol ($p<0.0001$), flatter late and overall decline slopes ($p<0.0001$ and $p=0.0006$, respectively), and higher bedtime cortisol levels ($p=0.0005$). The diurnal cortisol curve of included vs. excluded groups of participants is shown in Figure 2. The figure depicts the plot means with standard error bars of cortisol by 6 time points for those who wake up before 11am vs those who wake up after 11 am. Participants with wake-up time after 11am had a flatter cortisol curve over the course of the 6 measurements compared to participants that woke up prior to 11am (Figure 2).

Among whites, we found that a 1 unit increase in log CAR was associated with a 53% lower odds of incident diabetes over a ten-year period after full adjustment for covariates (OR: 0.47, 95% CI: 0.24–0.90). Additionally, a 1-SD flattening of the late decline slope (flattening of the slope) was associated with 5-fold higher odds of T2D among whites in the fully adjusted model (OR: 5.16, 95% CI: 1.32–20.20). There was some evidence of interaction between race and CAR ($p=0.04$, unadjusted Model 0) and between race and late decline slope ($p=0.04$, fully adjusted Model). Among AAs, there was no evidence of associations between baseline diurnal cortisol curve features with incident diabetes. The interaction term was non-significant across all models of the remaining diurnal cortisol curve components (Table 2).

In Table 3, following the exclusion of participants who woke up after 11 A.M, a 1 unit increase in log CAR was associated with a 52% lower odds of incident T2D in the fully adjusted model (OR 0.48: 95% CI 0.25–0.94) among whites. The association of late decline slope with incident diabetes was in the same direction but was non-significant among whites (OR 3.02: 95% CI 0.65, 13.96). No significant associations were found among AA participants and the interaction term for race was non-significant in all models across all components of the diurnal cortisol curve.

4. Discussion:

In CARDIA, a large biracial community-based cohort study with well-characterized data on salivary cortisol and diabetes status, this is the first report of the association of diurnal cortisol curve features with incident diabetes among whites and AAs. In this analysis, among whites a robust CAR at baseline was associated with significantly lower odds of T2D, and a flatter late decline slope was associated with higher risk of incident T2D, which was attenuated after excluding participants that woke-up after 11 A.M. Notably, significant

associations between components of the diurnal cortisol curve and incident T2D were not directly evident among AA participants.

To our knowledge, this is the first analysis to report that a robust CAR among whites is associated with lower odds of T2D. The result is directionally congruent with previous cross-sectional investigations revealing that an attenuated CAR is associated with perturbations in glycemic control. A blunted CAR is associated with a trend towards elevated insulin and HOMA-IR [41]. Furthermore, individuals with T2D exhibit blunted CARs compared to those without diabetes, which may be influenced by reductions in hippocampal volume [1,42]. The two previous studies that examined diurnal salivary cortisol curve features and risk of T2D were performed among majority older, white participants in the Longitudinal Aging Study Amsterdam (LASA) and Whitehall II cohorts. In the former, a higher evening salivary cortisol was associated with the development of T2D in women over a period of 6–7.5 years [23]. In the Whitehall II study, elevated evening salivary cortisol levels at baseline were associated with incident T2D over 10 years of follow-up [10]. Furthermore, those with flatter decline slopes and higher bedtime salivary cortisol were more likely to exhibit impaired fasting glucose or develop incident T2D [10]. In conjunction with these previous investigations, our results support the hypothesis that a more dynamic diurnal cortisol curve may be protective of dysglycemia, while a general flattening of the curve is associated with the impairment of glucose metabolism among whites. These prior studies and ours further elucidate the hypothesized temporality of the relationship between changes in the diurnal cortisol profile and diabetes—suggesting that changes to the diurnal cortisol profile precede the development of diabetes.

Our analysis does not support a relationship between diurnal cortisol curve features and the development of T2D among AAs. While we did not observe any strongly significant relationships with respect to the longitudinal development of T2D, cross-sectional findings in the Multi-Ethnic Study of Atherosclerosis (MESA) suggest that a flatter diurnal cortisol curve is associated with impaired glucose control among those who already have T2D in a mixed cohort of whites, AAs and Hispanic Americans [11]. Additionally, morning serum cortisol is cross-sectionally associated with higher FPG, but not HbA1c among AAs without T2D and associated with higher FPG and HbA1c among those with T2D in the Jackson Heart Study [43]. These results indicate that the impact of cortisol may become more pronounced following the development of dysglycemia among AAs.

The direct pathological effects of cortisol and excessive HPA-axis activity on the development of insulin resistance and T2D are well-characterized. HPA-axis stimulation occurs alongside an increase in sympathetic nervous system (SNS) activity, resulting in the release of catecholamine and inflammatory cytokines including TNF-alpha, which promotes insulin resistance in skeletal muscle and dose-dependently upregulates 11β-HSD1 in visceral adipose tissue [44–48]. Cortisol directly impairs insulin signaling in skeletal muscle and liberates free fatty acids, both of which directly leads to insulin resistance [49,50]. Furthermore, cortisol promotes hyperglycemia via increasing gluconeogenesis in the liver and inhibiting insulin secretion in rodent beta-cells [51]. Additionally, the upregulation of 11β-HSD1 activity in visceral fat is significantly correlated with visceral fat cell size [52]. The local activity of cortisol at the adipocyte promotes the redistribution of adipose tissue

from the periphery to central depots due to a relative overexpression of glucocorticoid receptors in visceral compared to subcutaneous adipose tissue [4]. Cortisol thus supports the development of visceral obesity, which is strongly associated with metabolic syndrome and T2D [53,54].

The majority of HPA-axis dysregulation likely stems from multifactorial progressive disturbances which accumulate throughout a lifetime. Overall stress burden stemming from various sources may also be linked to improper HPA-axis function, leading to a general flattening of the diurnal cortisol curve across the day [7]. Disruptions in sleep and the circadian rhythm may be another factor contributing to detrimental changes in HPA-axis function. Six consecutive nights of sleep restriction caused significant elevations in bedtime salivary cortisol and SNS activity in healthy men [55]. In addition, glucose tolerance decreases with sleep restriction, a finding which has been replicated in multiple investigations [56–58]. Disruption in circadian rhythms shares many deleterious effects on metabolic health as those seen in states of excessive cortisol production [59]. The molecular circadian pacemaker clock system and glucocorticoids are deeply intertwined.

Glucocorticoids are known to modulate the expression of peripheral clock genes, several of which contain glucocorticoid response elements (GREs) in their regulatory regions. The diurnal rhythm of cortisol thus serves a significant role in mediating synchronization of central and peripheral clocks [8]. Dysregulation of the diurnal rhythm stemming from multiple factors such as shift work [60], shortened sleep [14] or psychosocial stressors [16] may lead to de-coupling of the central and peripheral circadian cycles and ultimately metabolic disturbances. Perturbation of the circadian rhythm may partly explain the additional significant association observed between the late decline slope and incident diabetes when individuals waking up later than 11 A.M were included in the analysis. We show that a flattening of late decline slope is associated with increased odds of T2DM, which remained significant after adjustment for BMI among whites. The differences in associations dependent on the inclusion of those waking up after 11 A.M has implications for the extant literature and future investigations. Previous studies investigating cortisol and incident diabetes do not address inclusion based on wake-up times, which may have impacted the associations found [10,23]. Future studies of the diurnal cortisol features and various outcomes should take into consideration the significant differences in profiles based on wake-up time (Figure 2).

The baseline racial differences in cortisol curve features with AAs having a lower wake-up, flatter late decline slope and higher bedtime cortisol are consistent with the extant literature showing that AAs have flatter slopes than whites [24,25]. Interestingly, although AA participants had flatter late decline slopes, no significant associations between any decline slope features and incident diabetes were apparent among AAs. Higher baseline risk of incident diabetes in AAs may be one source of the non-significant findings in AAs. Compared to whites, AAs had higher fasting insulin, body mass index, and waist circumference with higher rates of smoking and depressive symptoms at baseline. Over the ten-year observational period, AAs had more than double the incidence of diabetes. Additional risk factors, in this case a blunted CAR or flatter diurnal cortisol curve, may impart less risk at the margin for individuals who are at high compared to low baseline risk.

Our group has previously shown this phenomenon with respect to the association of modifiable lifestyle risk factors with incident diabetes [61,62]. The lack of significant findings among AAs may also be a result of confounding via unobserved variables such as sleep duration or discrimination. Short sleep duration is associated with both flatter decline slopes and risk of diabetes [14,63]. Discrimination is associated with a flattening of the diurnal cortisol curve and greater risk of incident diabetes [16,64]. Thus, the higher baseline risk of incident diabetes in AAs and unmeasured confounders, including sleep and stress, may have led to the non-significant findings in AAs.

Our study has several strengths. To our knowledge, it is the first to perform a longitudinal analysis examining components of the diurnal cortisol curve and incident diabetes in a middle-aged biracial cohort. Participants were recruited from two different metropolitan areas (Chicago and Oakland), which increases external validity of the findings. The longitudinal nature of the study allows us to make greater inferences regarding the temporality of the relationship observed. The study includes an assessment of diabetes with ascertainment of anti-diabetic medication status and biological assessment of glucose. Furthermore, we were able to control for various confounders that are known to modulate cortisol activity and are associated with T2D. Even with these strengths, our findings should be interpreted in the context of the following limitations. First, the diagnostic criteria for T2D did not include oral glucose tolerance testing or HbA1c, thus we may have misclassified some participants with undiagnosed T2D. Second, all samples of salivary cortisol were collected on a single day and cortisol was not collected throughout the night, thus we are unable to evaluate a full 24-hour diurnal cortisol cycle. Third, the statistical associations were interpreted without adjustment for multiple comparisons, consistent with previous analyses [10,23]. Typical multiple comparison corrections assume that tests are independent and too conservative for correlated hypotheses as we have here. Hence, some caution is warranted in the interpretation of our study results. Fourth, while participants were provided with alarm watches to promote the targeted sampling regimen, it is important to note that the CAR is highly sensitive to sampling time [65]. We cannot rule out the possibility that the CAR was inaccurately measured among a subset of participants. Finally, due to the nature of observational studies, we cannot conclude that a causal relationship exists between perturbations in components of the diurnal cortisol profile and the development of T2DM.

5. Conclusion

In this novel longitudinal analysis examining the association of diurnal cortisol curve features with incident T2D in a middle-aged, biracial cohort, a robust CAR was associated with lower odds of incident T2D among whites. Additionally, a flatter late decline slope was associated with higher odds of T2D among whites when individuals are included independent of wake-up time. In AAs, associations between diurnal cortisol curve features and incident T2D were not apparent. Thus, the diurnal cortisol curve may represent a potential target for diabetes prevention but with potential racial/ethnic variation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the other investigators, the staff, and the participants of CARDIA for their valuable contributions. The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201800005I & HHSN268201800007I), Northwestern University (HHSN268201800003I), University of Minnesota (HHSN268201800006I), and Kaiser Foundation Research Institute (HHSN268201800004I). This manuscript has been reviewed by CARDIA for scientific content. BK was supported by a research grant from the Endocrine Society Summer Research Fellowship Program. JJJ was supported by K23DK117041 from the National Institute of Diabetes and Digestive and Kidney Diseases (USA) and The Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program ID# 76236. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. The graphical abstract was created with BioRender.com.

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Highlights

- Examined the association of the cortisol curve with incident diabetes over 10 years
- Cortisol awakening response was inversely associated with diabetes in whites
- Late decline slope was positively associated with diabetes in whites
- Cortisol features were not associated with diabetes in African Americans

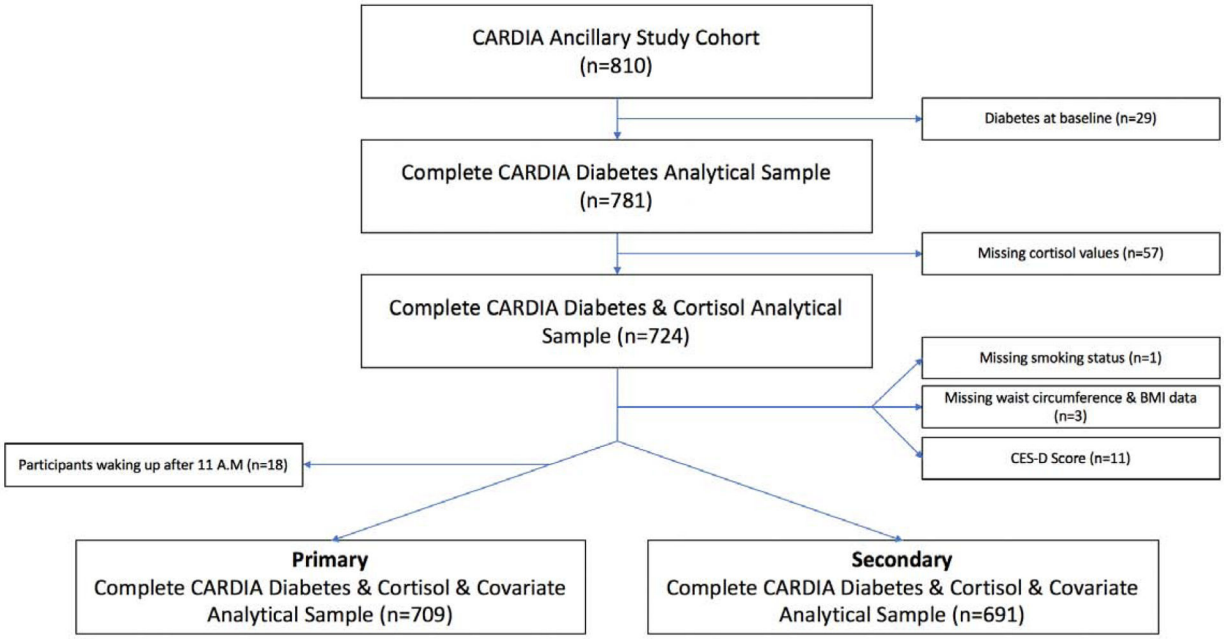

Figure 1.

Exclusion Cascade for Participants in this Analysis

The CARDIA ancillary cortisol study cohort included 810 participants. Subjects were excluded on the basis of having diabetes at baseline (n=29) or had missing values for the following variables: diurnal cortisol profile components (n=57), smoking status (n=1), body mass index (BMI) (n=3) and Center for Epidemiologic Studies Depression scale (CES-D) score (n=11). The primary analytical data set included 709 participants. Individuals waking up after 11 A.M were excluded (n=18) for the secondary analysis, which ultimately included 691 individuals.

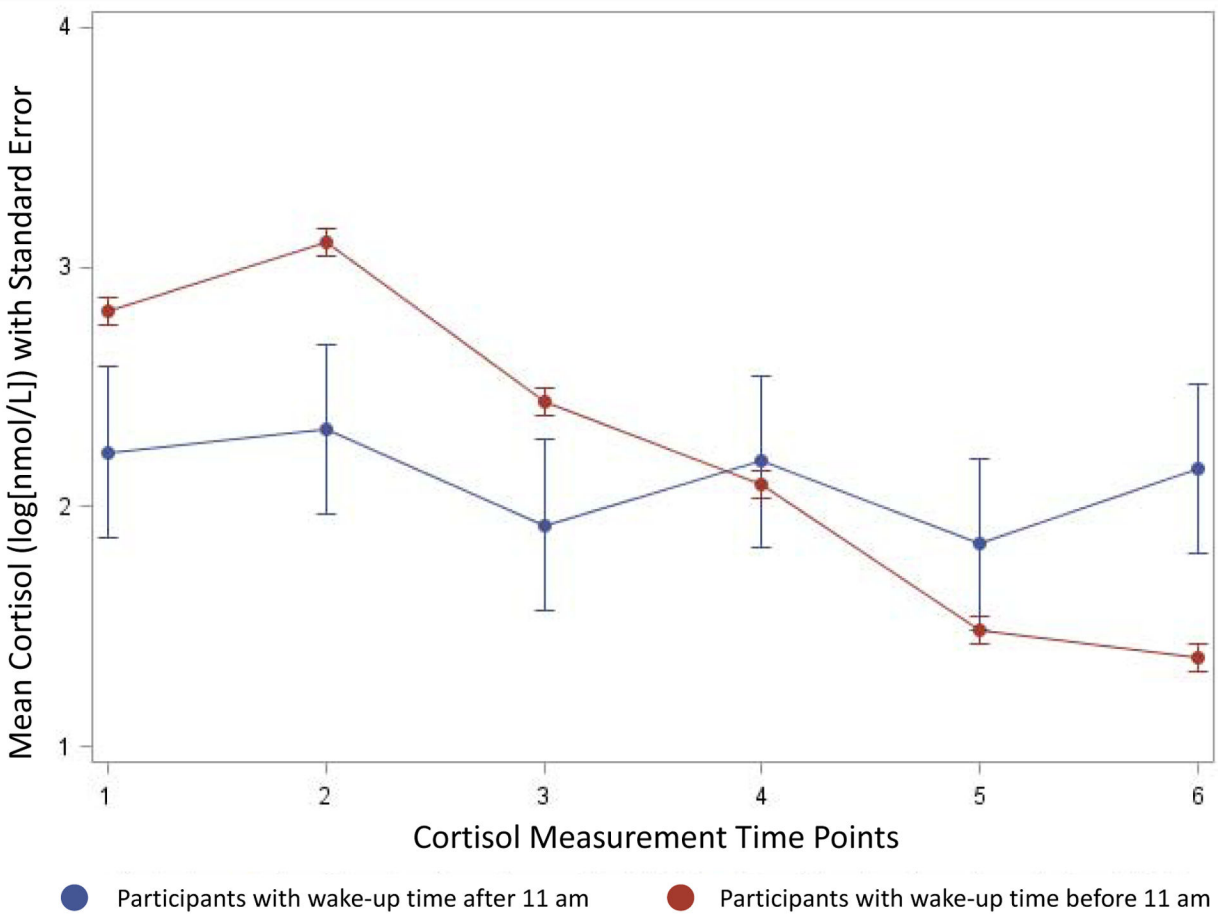

Figure 2:

Diurnal Cortisol Profile Based on Wake-Up Time

The figure depicts the plot means with standard error bars of cortisol by 6 time points for those who wake up before 11am vs those who wake up after 11 am. Participants with wake-up time after 11am had a flatter cortisol curve over the course of the 6 measurements compared to participants that woke up prior to 11am.

Time points—1: immediately post-awakening, 2: 45 minutes, 3: 2.5 hours, 4: 8 hours, 5: 12 hours, 6: bedtime

Table 1:

Baseline Characteristics of Participants by Race/Ethnicity

Characteristic[a,b]	All	African American	White	p-value
Participants - n (%)	709 (100%)	376 (53%)	333 (47%)	
Demographic				
Age - years	39.96 ± 3.63	39.55 ± 3.75	40.43 ± 3.44	0.0014
Female sex - n (%)	414 (58%)	232 (62%)	182 (55%)	0.0574
Race/Ethnicity - n (%)[c]				
White	333 (47%)			
African American	376 (53%)			
Years of Education	14.96 ± 2.47	14.12 ± 2.20	15.90 ± 2.41	<0.0001
Clinical				
Fasting glucose (mg/dL)	83.56 ± 9.85	84.17 ± 10.33	82.87 ± 9.26	0.0797
Fasting Insulin (pmol/L)	14.24 ± 10.73	15.84 ± 11.26	12.45 ± 9.81	<0.0001
Body mass index[d]	29.25 ± 7.24	31.23 ± 7.54	27.02 ± 6.16	<0.0001
Waist circumference (cm)	89.11 ± 14.99	91.65 ± 14.97	86.23 ± 14.49	<0.0001
Beta-blocker - n (%)	14 (2%)	8 (2%)	6 (2%)	0.7556
Steroid - n (%)	34 (5%)	21 (6%)	13 (4%)	0.2957
Current Smoking - n (%)	125 (18%)	89 (24%)	36 (11%)	<0.0001
Center for Epidemiologic Studies Depression Scale Score	9.19 ± 7.75	10.44 ± 8.20	7.79 ± 6.96	<0.0001
Cortisol Features[e]				
Wake-up Cortisol	2.80 ± 0.62	2.74 ± 0.66	2.88 ± 0.56	0.0035
Cortisol Awakening Response	0.28 ± 0.67	0.29 ± 0.67	0.27 ± 0.66	0.7132
Early Decline Slope	−0.40 ± 1.71	−0.46 ± 2.33	−0.33 ± 0.33	0.2801
Late Decline Slope	−0.07 ± 0.20	−0.05 ± 0.20	−0.10 ± 0.21	0.0002
Overall Decline Slope	−0.10 ± 0.21	−0.08 ± 0.24	−0.11 ± 0.18	0.0728
Bedtime Cortisol	1.39 ± 2.36	1.64 ±1.77	1.11 ± 2.87	0.0037
Total Area-Under-the-Curve (16-hours) Cortisol	1.99 ± 0.83	1.98 ± 0.92	1.99 ± 0.71	0.8553
Dysglycemia				
Normal - n (%)	650 (93%)	335 (91 %)	315 (96%)	0.0133
Impaired Fasting Glucose - n (%)[f]	47 (7%)	33 (9%)	14 (4%)	0.0133
HOMA-Beta[g]	4.75 ± 0.52	4.84 ± 0.53	4.64 ± 0.49	<0.0001
HOMA-IR[g]	0.64 ± 0.60	0.75 ± 0.59	0.51 ± 0.58	<0.0001

[a] Data are reported as means ± SD or as numbers with percentages.

[b] p-values reported for chi-square tests (categorical variables) and for two-sample t-test (continuous variables)

[c] Race was self-reported.

[d] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[e] Cortisol features were calculated using log-transformed cortisol values (unit: log[nmol/L]);

[f] Impaired Fasting Glucose = 100–125 mg/dL

[g] Homeostatic model assessment (HOMA) of β-cell function and insulin resistance (IR) are log-transformed.

Table 2.

Odds Ratios of Incident Diabetes over 10 years in CARDIA

Variable, Group, Interaction[a]	Total #, Incident Cases	Model 0 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Wake-up Cortisol				
Whites	333, 19	0.90 (0.40, 2.05)	0.85 (0.37, 1.95)	0.82 (0.36, 1.87)
African Americans	376, 48	1.12 (0.71, 1.76)	1.16 (0.73, 1.84)	1.16 (0.73, 1.84)
Interaction		P=0.6548	P= 0.5242	P= 0.4793
Cortisol Awakening Response				
Whites	333, 19	**0.39 (0.21, 0.75)**	**0.43 (0.22, 0.82)**	**0.47 (0.24, 0.90)**
African Americans	376, 48	0.90 (0.57, 1.42)	0.86 (0.54, 1.36)	0.88 (0.55, 1.40)
Interaction		P= 0.0396	P= 0.0912	p=0.1238
Early Decline Slope[b]				
Whites	333, 19	3.98 (0.45, 34.79)	3.57 (0.41, 31.4)	3.09 (0.35, 27.67)
African Americans	376, 48	0.97 (0.81, 1.15)	0.96 (0.80, 1.15)	0.97 (0.81, 1.16)
Interaction		P=0.2024	P=0.2388	p=0.2998
Late Decline Slope[b]				
Whites	333, 19	**6.94 (1.81, 26.66)**	**6.35 (1.58, 25.48)**	**5.16 (1.32, 20.20)**
African Americans	376, 48	1.23 (0.96, 1.58)	1.23 (0.95, 1.59)	1.21 (0.93, 1.58)
Interaction		P=0.0132	P=0.0226	p=0.0414
Bedtime Cortisol				
Whites	333, 19	1.43 (0.86, 2.36)	1.39 (0.83, 2.34)	1.33 (0.81, 2.20)
African Americans	376, 48	1.24 (0.90, 1.71)	1.23 (0.88, 1.71)	1.25 (0.89, 1.75)
Interaction		P=0.6514	P=0.6820	p=0.8376
Overall Decline Slope[b]				
Whites	333, 19	2.54 (0.78, 8.24)	2.61 (0.79, 8.63)	2.47 (0.76, 8)
African Americans	376, 48	0.96 (0.77, 1.21)	0.95 (0.76, 1.19)	0.96 (0.76, 1.21)
Interaction		P=0.1137	P= 0.1036	p=0.1203
Total AUC (16-Hours) Cortisol				
Whites	333, 19	0.97 (0.52, 1.81)	0.90 (0.47, 1.71)	0.91 (0.49, 1.70)
African Americans	376, 48	1.07 (0.74, 1.56)	1.04 (0.72, 1.50)	1.05 (0.70, 1.57)
Interaction		P=0.7845	P=0.6931	p=0.7032

[a] logistic regression models to calculate the odds ratios

[b] Slopes were standardized using z-scores

Model 0: Odds ratio of cortisol feature with incident diabetes (unadjusted)

Model 1: Odds ratio of cortisol feature with incident diabetes (adjusted for age, sex, race, education, CES-D score, beta-blocker or steroid [inhaled or oral] usage and cigarette smoking).

Model 2: Odds ratio of cortisol feature with incident diabetes (Model 1 + categorical BMI)

Bold = $p<0.05$

Table 3.

Odds Ratios of Incident Diabetes over 10 years in CARDIA excluding Participants with Wake-up Time after 11am

Variable, Group, Interaction[a]	Total #, Incident Cases	Model 0 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Wake-up Cortisol				
Whites	327, 17	1.07 (0.45, 2.56)	1.01 (0.42, 2.46)	0.96 (0.39, 2.32)
African Americans	364, 48	1.07 (0.67, 1.69)	1.09 (0.68, 1.75)	1.10 (0.69, 1.75)
Interaction		P=0.9907	P= 0.8829	P= 0.7859
Cortisol Awakening Response				
Whites	327, 17	**0.41 (0.21, 0.79)**	**0.44 (0.23, 0.86)**	**0.48 (0.25, 0.94)**
African Americans	364, 48	0.89 (0.57, 1.40)	0.86 (0.54, 1.37)	0.89 (0.56, 1.42)
Interaction		P= 0.0550	P= 0.1101	p=0.1377
Early Decline Slope[b]				
Whites	327, 17	5.71 (0.58, 55.83)	5.04 (0.51, 49.54)	4.55 (0.45, 46.47)
African Americans	364, 48	0.97 (0.81, 1.16)	0.97 (0.81, 1.16)	0.97 (0.81, 1.17)
Interaction		P=0.1285	P=0.1583	p=0.1937
Late Decline Slope[b]				
Whites	327, 17	3.88 (0.86, 17.6)	3.53 (0.74, 16.86)	3.02 (0.65, 13.96)
African Americans	364, 48	1.24 (0.96, 1.6)	1.23 (0.94, 1.6)	1.22 (0.93, 1.59)
Interaction		P=0.1441	P=0.1908	p=0.2492
Bedtime Cortisol				
Whites	327, 17	1.24 (0.72, 2.14)	1.21 (0.70, 2.10)	1.18 (0.70, 1.98)
African Americans	364, 48	1.26 (0.92, 1.74)	1.25 (0.90, 1.74)	1.28 (0.92, 1.79)
Interaction		P=0.9598	P=0.9104	p=0.7894
Overall Decline Slope[b]				
Whites	327, 17	1.52 (0.44, 5.28)	1.55 (0.42, 5.72)	1.57 (0.43, 5.73)
African Americans	364, 48	0.97 (0.77, 1.23)	0.97 (0.76, 1.23)	0.97 (0.76, 1.25)
Interaction		P=0.4915	P= 0.4843	p=0.4803
Total AUC (16-Hours) Cortisol				
Whites	327, 17	0.97 (0.50, 1.85)	0.90 (0.46, 1.75)	0.91 (0.48, 1.74)
African Americans	364, 48	1.07 (0.74, 1.56)	1.05 (0.73, 1.52)	1.07 (0.71, 1.59)
Interaction		P=0.7792	P=0.6783	p=0.6885

[a] logistic regression models to calculate the odds ratios

[b] Slopes were standardized using z-scores

Model 0: Odds ratio of cortisol feature with incident diabetes (unadjusted)

Model 1: Odds ratio of cortisol feature with incident diabetes (adjusted for age, sex, race, education, CES-D score, beta-blocker or steroid [inhaled or oral] usage and cigarette smoking).

Model 2: Odds ratio of cortisol feature with incident diabetes (Model 1 + categorical BMI)

Bold = $p<0.05$